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INVENTOR(S)

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TITLE OF THE INVENTION

DNA SEQUENCING METHOD AND SYSTEM

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Respectfully submitted,

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MICRO-NOZZLE, NANO-NOZZLE, MANUFACTURING METHODS THEREFOR, APPLICATIONS THEREFOR

by Sadeg M. Faris

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application Serial Number 60/446,296 filed on February 10, 2003, entitled "Micro-Nozzle, Nano-Nozzle, Manufacturing Methods Therefor, Applications Therefore, Including Nanolithography and Ultra Fast Real Time DNA Sequencing," which is herein incorporated by reference.

Field Of The Invention

The present invention relates to micro-nozzles and nano-nozzles, and methods of manufacturing micro-nozzles and nano-nozzles.

Background Information

Understanding and harnessing properties of nanotechnology has and will continue to result in 21st Century breakthroughs. Products such as nano-scale computing devices, nanotechnology based fibers stronger than steel, and advanced biochemical sensors are just a few of the astounding applications of nanotechnology.

One limitation in nanotechnology is processing devices used to handle, dispense, detect, or otherwise manipulate nanoparticles. While nozzles are known for applications such as inkjet printing and other deposition processes, nano-scale nozzles are generally unknown.

Thus, there remains a need in the art for improved sub-micron and nanoscale nozzles, and efficient and reliable methods of manufacturing sub-micron and nanoscale

nozzles.

SUMMARY OF THE INVENTION

The above-discussed and other problems and deficiencies of the prior art are overcome or alleviated by the several methods and apparatus of the present invention for micro and nano nozzles. A nozzle structure is provided comprising a monolithic body having an array of nozzles. The nozzles having openings with sectional openings having heights of about 100 nm or less. The nozzles are generally associated with one or more well structures.

Applications of the herein described nozzle include, but are not limited to, nanolithography, protein and DNA sequencing, and nano-chemistry, including synthesis and analysis.

The above-discussed and other features and advantages of the present invention will be appreciated and understood by those skilled in the art from the following detailed description and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a portion of a device having a plurality of arrays of nozzles;

Figure 2 depicts a starting multiple layered substrate used in certain embodiments herein;

Figures 3A-B show plural devices formed on a wafer to be formed into nozzles;

Figures 3C-D and 4 show details of the devices;

Figures 5A-B show a processing step to apply a layer to the device;

Figure 6 shows removal of the device layer from a substrate;

Figure 7 shows stacking of plural devices (or device layers);

Figure 8 shows cut lines for forming nozzles from the stack of devices;

Figures 9-11 show an embodiment of one method of forming nozzle openings;

Figures 12-13 show anther embodiment of one method of forming nozzle openings;

Figures 14-15 show anther embodiment of one method of forming nozzle openings;

Figures 16-17 show a stack of nozzles with spacer layers therebetween;

Figure 18 shows an enlarged view of a section of a nozzle;

Figure 19 shows an enlarged view of a section of a nozzle detailing a grind stop;

Figures 20A shows an enlarged cross section of stacked layers used to form the micro and nano nozzles;

Figure 20B shows a front view of a nozzle;

Figure 21 is another view of the nozzle depicting possible regions for electrodes or other nozzle features;

Figures 22A-D show an exemplary method of making nozzles with openings having various conductors (e.g., serving as electrodes) thereabout;

Figures 23A-C show an exemplary method of making nozzles with sub-layers;

Figures 24A-D show one exemplary array of nozzles;

Figures 25A-D show another exemplary array of nozzles;

Figures 26A-D show a further example of an array of nozzles;

Figures 27A-D show another example of an array of nozzles;

Figures 28A-B show a lithography application of the herein nozzles;

Figures 29A-B show another lithography application of the herein nozzles;

Figure 30 is an overview of a sequencing application of the herein nozzles;

Figure 31 shows arrays of the herein nozzles;

Figure 32 shows an ultra fast DNA sequencing system;

Figure 33 is a schematic of major components of the ultra-fast DNA sequencing system;

Figure 34 is a top view of the ultra-fast DNA sequencing system;

Figures 35A-B detail each channel of the sequencing system;

Figure 36 shows section views of the sequencing process;

Figure 37 shows detailed views of hybridization events;

Figure 38 shows all possible 16 combinations of A,T,G and C for sequencing;

Figure 39 shows a reference position and precision nanometer metrology prove and system; and

Figure 40 shows stepped motion of a strand to be sequenced relative to the probe of Figure 39.

DETAILED DESCRIPTION OF THE ILLUSTRATIVE EMBODIMENTS

Herein disclosed are nano-nozzles and methods of manufacturing nano-nozzles. With the disclosed methods, it is possible to create nozzles with opening dimensions on the order of nanometers. Further, it is possible to make such nozzles in arrays with exact spacing therebetween. Such features enable molecular level dispersion, precise material deposition, molecular level detection, and other nano-scale processes. Referring to Figure 1, a portion of a device 10 having a plurality of arrays 12 of nozzles 14 is depicted. Note that the dimensions of such nozzles may be on the order of a few nanometers (e.g., 5 nm) or greater, depending on the desired application. Further, the

arrays may be spaced apart by 10s of nanometers to several micros apart.

The present method of manufacturing nozzles may be enhanced with the use of Applicant's multi-layered manufacturing methods, as described in U.S. Non-provisional Application Serial Nos. 09/950,909, filed September 12, 2001 entitled "Thin films and Production Methods Thereof"; 10/222,439, filed August 15, 2002 entitled "Mems And Method Of Manufacturing Mems"; 10/017,186 filed December 7, 2001 entitled "Device And Method For Handling Fragile Objects, And Manufacturing Method Thereof"; and PCT Application Serial No. PCT/US03/37304 filed November 20, 2003 and entitled "Three Dimensional Device Assembly and Production Methods Thereof"; all of which are incorporated by reference herein. However, other types of semiconductor and/or thin film processing may be employed.

Referring to Figure 2, a starting multiple layered substrate 100 is shown. The substrate 100 may be, in certain preferred embodiments, a wafer for processing thousands or even millions of nozzle arrays.

The multiple layered substrate 100 includes a first device layer 110 selectively bonded to a second substrate layer 120, having strongly bonded regions 3 and weakly bonded regions 4. Using the techniques described in the above-mentioned patent applications, or other suitable wafer processing and handling techniques, the first layer 110, intended for having one or more useful structures processed therein or therein, may readily be removed from the second substrate layer 120 (which serves as mechanical support during device processing) with little or no damage to the structure(s) formed (including wells or other subtractions to the layer 110) in or on the device layer 110.

Layers 110 and 120 may be the same or different materials, and may include

materials including, but not limited to, plastics (e.g., polycarbonate), insulators, semiconductor, metal conductors, monocrystalline, amorphous, noncrystalline, biological (e.g., DNA based films) or a combination comprising at least one of the foregoing various types of materials. For example, specific types of materials include silicon (e.g., monocrystalline, polycrystalline, noncrystalline, polysilicon, and derivatives such as Si3N4, SiC, SiO2), GaAs, InP, CdSe, CdTe, SiGe, GaAsP, GaN, SiC, GaAlAs, InAs, AlGaSb, InGaAs, ZnS, AlN, TiN, other group IIIA-VA materials, group IIB materials, group VIA materials, sapphire, quartz (crystal or glass), diamond, silica and/or silicate based material, or any combination comprising at least one of the foregoing materials. Of course, processing of other types of materials may benefit from the process described herein to provide multiple layer substrates 100 of desired composition. Preferred materials which are particularly suitable for the herein described methods include semiconductor material (e.g., silicon) as layer 110, and semiconductor material (e.g., silicon) as layer 120. Other combinations include, but are not limited to; semiconductor (layer 110) on glass (layer 120); semiconductor (layer 110) on silicon carbide (layer 120); semiconductor (layer 110) on sapphire (layer 120); GaN (layer 110) on sapphire (layer 120); GaN (layer 110) on glass (layer 120); GaN (layer 110) on silicon carbide (layer 120); plastic (layer 110) on plastic (layer 120), wherein layers 110 and 120 may be the same or different plastics; and plastic (layer 110) on glass (layer 120).

Layers 110 and 120 may be derived from various sources, including wafers or fluid material deposited to form films and/or substrate structures. Where the starting material is in the form of a wafer, any conventional process may be used to derive layers 110 and/or 120. For example, layer 120 may consist of a wafer, and layer 110 may

comprise a portion of the same or different wafer. The portion of the wafer constituting layer 110 may be derived from mechanical thinning (e.g., mechanical grinding, cutting, polishing; chemical-mechanical polishing; polish-stop; or combinations including at least one of the foregoing), cleavage propagation, ion implantation followed by mechanical separation (e.g., cleavage propagation, normal to the plane of structure 100, parallel to the plane of structure 100, in a peeling direction, or a combination thereof), ion implantation followed by heat, light, and/or pressure induced layer splitting), chemical etching, or the like. Further, either or both layers 110 and 120 may be deposited or grown, for example by chemical vapor deposition, epitaxial growth methods, or the like.

An important benefit of the instant method and resulting multiple layer substrate 100, or thin film (e.g., layer 110) derived from the multiple layer substrate 100 is that the structures are formed in or upon the weak bond regions 3. This substantially minimizes or eliminates likelihood of damage to the useful structures when the layer 110 is removed from layer 120. The debonding step generally requires intrusion (e.g., with ion implantation), force application, or other techniques required to debond layers 110 and 120. Since, in certain embodiments, the structures are in or upon regions 3 that do not need local intrusion, force application, or other process steps that may damage, reparably or irreparable, the structures, the layer 110 may be removed, and structures derived therefrom, without subsequent processing to repair the structures. The strong bond regions 4 generally not have structures thereon, therefore these regions 4 may be subjected to intrusion or force without damage to the structures.

The layer 110 may be removed as a self supported film or a supported film. For example, handles are commonly employed for attachment to layer 110 such that layer

110 may be removed from layer 120, and remain supported by the handle. Generally, the handle may be used to subsequently place the film or a portion thereof (e.g., having one or more useful structures) on an intended substrate, another processed film, or alternatively remain on the handle.

Referring now to Figures 3A and 3B, top isometric and sectional views, respectively, are provided of a selectively bonded substrate 100 having a plurality of wells 130 formed in the weakly bonded regions of the selectively bonded substrate 100. Note that the pattern of weak bond regions and strong bond regions may vary, as described in aforementioned U.S.S.N. 09/950,909 and PCT/US03/37304. However, it is preferred that all of the wells are formed at the weak bond regions of the device layer 110 and supported during processing by the support layer 120.

Figures 3C and 3D show plan and sectional views, respectively, of a single well 130 formed in the device layer 110 described above. Referring to Figure 3C, the intersecting region between the dashed lines and the walls 132 of the wells 130 shows regions wherein nozzles 14 (as depicted in Figure 1) may be processed in certain embodiments, as described hereinafter. In other embodiments, there may be only one intended region for processing nozzles (e.g., on the left or right sides as shown in Figures 3C and 3D).

In further embodiments, the wells may be formed only at the intended nozzle region, e.g., resembling grooves having the thickness shown by the dashed lines.

Referring also to Figure 4, the etched well 130 generally has angular walls 132, the function of which will be readily apparent. Further, the center recessed portion 134 of the etched well will become part of a reservoir of the nozzles. At the top surface of the

device layer 110 adjacent the outer ends of the angular walls 132 are plateau regions, which ultimately may be part of the inside wall of the nozzles as described herein.

The width (i.e., the y direction as shown in Figures 9-11) of the nozzles 14 may be the same or different from the width of the wells. In certain embodiments, it may be desirable to provide wells having widths larger than that of the nozzle to increase the material capacity of the well while maintaining the nozzle dimensions as small as possible.

Referring now to Figure 4, a layer 110 (e.g., having thickness on the order of 10 - 100 nm for nano-nozzles used in applications where nozzle tips of a few nanometers are desired) is selectively bonded to a support layer 120 as described with respect to Figure 2 and in aforementioned USSN 09/950,909 and PCT/US03/37304. A region of reservoir 130 is etched away or otherwise removed from a region of the device layer in the weak bond region 3. Suitable nano-scale material subtraction methods may be used.

Referring now to Figure 5A, a layer 138 (e.g., 5-10 nm) of material, preferably material that is easily removable by etching or other subtractive methods, is deposited on the wafer. This material may be conductive, such as copper, silicon oxide, aluminum, or other suitable materials. This space will later become the opening for the nozzle.

Referring to Figure 5B, a fill 140 may optionally be incorporated, also of easily removable material in certain embodiments. The material optionally used to fill the wells during processing and stacking may be the same or different from the material used at the plateaus (that will form nozzle walls).

Since the device layer including the etched well having suitable material deposited thereon is generally positioned over the weak bond region 3 of the multiple

layered substrate 100, the device layer 110 may readily be removed form the support layer 120. For example, the strong bond regions 4 may be etched away by through etching (e.g., normal to the surface through the thickness of the device layer in the vicinity of the strong bond region), edge etching (parallel to the surface of the layers), ion implantation (preferably with suitable masking of the etched well and deposited material to form the nozzle, or by selective ion implantation), or other known techniques. Since the above techniques are generally performed at the strong bond regions 4 only, the etched well and material deposited in the weak bond regions 3 are easily released form the substrate, as schematically shown in Figure 5, for example with a handler 150.

Referring now to Figure 7, several layers 110 including etched wells 130 having material deposited 138 thereon (and optionally fill 140) may be stacked to form a structure 160. The structure 160 may further include a solid layer 162, e.g., to form a wall for the top-most nozzle as shown in Figure 7. Although in certain embodiments precise alignment may be desired at this point, certain embodiments may use relaxed alignment standards at this point, as will be apparent.

As shown in Figure 8, the wafer stack 160 can now be sliced in the middle along the line 164, creating two portions with exposed reservoirs. From the opposing side, these devices can also be sliced along the line 166. The end may be grinded and polished until it is very close to the etched away reservoir, but no less than the desired nozzle length.

Referring now to Figures 9 and 10, the deposited material 138 may be etched away, exposing an etched channel 168 (e.g., 5 nm opening when the material deposition layer is 5 nm). A material reservoir 170 (or region 170 for other purposes, depending on

the desired use of the nozzle structure) remains behind the opening 168. Each etched channel 168 is generally spaced apart by approximately the thickness of the device layer 110. Thus, a nozzle device 10 having plural openings 168 each associated with regions 170 is provided.

Alternatively, and referring to Figure 11, to form an opening less than the width of the entire edge, the outside portions may be masked 172 prior to etching the deposited material 138 to form openings 168'. Thus, a nozzle device 10' having plural openings 168' is provided.

In a further embodiment, and referring now to Figures 12 and 13, a nozzle device 180 (e.g., as describe herein), of a single layer, may be rotated approximately 90° with respect to the stack of layers 160 having layers 138 deposited therein at the locations of the nozzles. Etchant may be filled in the reservoir of the rotated nozzle structure 180, and the openings 182 of the nozzles may be formed. Using this technique, it is possible to create nozzles having approximately the same width and height (e.g., 5-10 nm by 5-10 nm). Thus, a nozzle device 10" having plural openings 168" is provided.

Referring now to Figures 14 and 15, another embodiment of a method of forming very small width nozzle diameters. As described with reference to Figures 9 and 10, the deposited material between layers may be etched away, exposing an etched channel (e.g., 5-10 nm high when the material deposition layer is 5-10 nm) spaced apart by approximately the thickness of the device layer.

These etched channels 168 may then be filled with an etchable material. For example, a nozzle device 180 as describe herein, of a single layer, may be rotated approximately 90° with respect to the stack of layers having material etched away at the

locations of the nozzles. An etchable material may be filled in the reservoir of the rotated nozzle structure, which is filled at the regions where the nozzles on the stack of layers are to be formed. The surrounding areas between the layers are then filled with a plug material. Then the etchable material in the nozzle region is etched away, exposing the nozzles 168'''. Using this technique, it is possible to create nozzles having approximately the same width and height (e.g., 5-10 nm by 5-10 nm). Thus, a nozzle device 10''' having plural openings 168''' is provided.

Note this etchable material should be selectively removable by an etchant (e.g., not removing the bulk material).

Referring now to Figures 16 and 17, a nozzle array 200 of the present invention is shown. Therein, one or more spacer layers 202 may be positioned between a desired number of to-be-formed channels, e.g., during stacking of the well structures.

Referring to Figure 18, an enlarged cross section of stacked layers 110 used to form the micro and nano nozzles having wells and tip portions as described herein, cut to desired tip length, is shown. The layers 138 have been processed to form the wells 130 and nozzle tip regions generally by deposition of a layer 138 of material capable of being selectively removed (e.g., etched) therein (the well) and thereon (the shelf at the top of the well), as described herein. The materials capable of being selectively removed for the plateau and and/or the well may be the same or different. The wells and plateaus have various dimensions that will characterize the nozzle array ultimately formed. The nozzle has a tip length NL, a tip opening height NO, and a period P.

Referring to Figure 19, an enlarged cross section of stacked layers used to form the micro and nano nozzles herein is shown, detailing grind stops 186 provided to

enhance the ability to control the nozzle length NL. In certain embodiments, it is desirable to minimize the nozzle length. A grind stop 186 is provided proximate the desired nozzle length. The grind stop may be provided during processing of the wells on the device layer. Further, the grind stops may further serve as alignment marks, e.g., as described in aforementioned PCT/US03/37304.

Referring to Figures 20A and 20B, an enlarged cross section of stacked layers used to form the micro and nano nozzles, and a front view of the nozzle, respectively, are shown. Note that in certain embodiments, the well 170 has a width (y direction) greater than that of the nozzle tip 168.

Note that in any of the herein described nozzles and nozzle arrays, associated structures may be provided. For example, in certain embodiments, one or more electrodes may be provided to facilitate material discharge, detection capabilities, etc. Further, one or more processors, micro or nano fluidic devices, micro or nano electromechanical devices, or any combination including the foregoing devices may be incorporated in a nozzle device. In certain preferred embodiments, electrodes are provided at the nozzle openings and/or wells, and an electrode controller and/or a microfluidic device (e.g., to feed or remove material from the nozzles) is associated with an array of nozzles.

Referring now to Figure 21, an enlarged view of a nozzle structure 200 is provided, viewing a nozzle opening 202. Nozzle opening 202 is generally positioned on a nozzle layer "N" between a top portion "A" and a bottom portion "B" (although top and bottom are considered to be relevant for the purpose of description herein only). To describe various embodiments of possible configurations, sections N, A and B have been

divided into descriptive sections. These descriptive sections may be actual discrete regions of different material, or in certain embodiments multiple descriptive sections may be of the same material and thus actually a uniform region, as will be apparent from the various embodiments herein.

A_A and B_B may be the same or different materials, such as insulator or semiconductor materials to provide the structure of the nozzle 200, electrically insulate the nozzle openings from one another, fluidly seal the openings from one another, or other functionality.

In certain embodiments, the descriptive sections A_L, A_C, A_R, N_L, N_R, B_L, B_C and B_R are all of the same materials as A_A and B_B.

Any combination of A_L, A_C, A_R, N_L, N_R, B_L, B_C and/or B_R may be provided in the form of conductors. For example, referring back to Figure 11, upon removal of the mask after etching the nozzle opening, a structure may be provided having A_L, A_C, A_R, B_L, B_C and B_R of the same materials as A_A and B_B, and N_L, N_R of conductive material.

Further, and referring now to Figures 22A-D, an exemplary method of making nozzles with openings having various conductors (e.g., serving as electrodes) thereabout is depicted. Figure 22A shows a starting section of a multiple layer substrate with layers 110 and 120 as described hereinabove. An etched well 130 generally has angular walls 132 and a center recessed portion 134. Plateau regions 136 form the opening walls or supports.

A layer 238 (e.g., 5-10 nm) of conductive material is deposited on the wafer. A removable fill material 240 may be provided in the well to facilitate layering. Referring to Figure 22B, a removable fill layer 242 is provided on the surface having the

conductive layer 238 and the optionally fill material 240. In this embodiment, the nozzle will be formed at the fill layer 242. Further, a conductive layer 244 is deposited or layered on the fill layer 242, forming a nozzle sub-structure 250.

Referring now to Figure 22C, a plurality of nozzle sub-structures 250 are aligned and stacked (e.g., as described above with respect to Figure 7). Referring to Figure 22D, nozzle openings 260 may be formed, e.g., according to one of the methods described above with respect to Figures 9-15, or other lithography or oxidation methods. The resulting structure may be one wherein AL, AC, AR, BL, BC and BR of conductive materials and NL, NR are of insulative material.

Further, one or more pairs of opposite descriptive sections may be conductive (e.g., electrodes), thereby enabling creation of fields across the nozzle opening. For example, NL and NR, AC and BC, AL and BR, AR and BL, AL,AR and BL, BR may all be electrode pairs to provide any desired functionality. Additionally, one or more conductive electrodes may be within the well regions, e.g., to provide electromotive forces to move materials.

Referring now to Figures 23A-C, an example of a method of manufacturing the herein described nozzles is shown whereby a plurality of sub-layers 302 form each layer 310. Wells 330 are processed through the layer 310 as shown in Figure 23B. Figure 23C shows nozzle openings 360 having plural sublayers 302 therearound. These sub-layers may be very useful, for example, where precise metrology is desired.

For example, in certain embodiments, the sub-layers 302 are formed to very precise tolerances, e.g., having thicknesses on the order of 0.5 to about 5 nanometers. When these sub-layers 302 are formed of differing materials (e.g., alternating between

insulator and semiconductor, semiconductor and conductor, or conductor and insulator), precise step motion may be enabled in the nozzle structures based on known dimensions of the nozzle sub-layers.

Figures 24A-D show a nozzle array formed according to embodiments of the present invention. The nozzle array includes, e.g., a 1 x 4 array (although it is understood that this may be scaled to any size n x m nozzles) of nozzles, as shown in Figure 24B (line b in 24A). These nozzles are associated with wells, as shown in Figure 24C (line c in 24A) having widths in the y direction greater than the widths of the nozzle tips. Figure 24D shows a sectional view of the nozzle array (line d in 25A).

Figures 25A-D show a nozzle array formed according to embodiments of the present invention. The nozzle array includes, e.g., a 4 x 4 array (although it is understood that this may be scaled to any size n x m nozzles) of nozzles, as shown in Figure 25B (line b in 25A). These nozzles are associated with wells, as shown in Figure 25C (line c in 25A), wherein the wells are formed having approximately the same widths in the y direction as that of the nozzle. Further, several nozzles are formed in each layer in the y direction. Figure 25D shows a sectional view of the nozzle array (line d in 25A).

Figure 26A shows a nozzle array formed according to embodiments of the present invention. The nozzle array includes, e.g., a 4 x 4 array (although it is understood that this may be scaled to any size n x m nozzles) of nozzles, as shown in Figure 26B (line b in Figure 26A). These nozzles are associated with a single well, as shown in Figure 26C (line c in Figure 26A). Figure 26D shows a sectional view of the nozzle array (line d in Figure 26A).

Figure 27A shows a nozzle array formed according to embodiments of the present

invention. The nozzle array includes, e.g., a 4 x 4 array (although it is understood that this may be scaled to any size n x m nozzles) of nozzles, as shown in Figure 27B (line b in Figure 27A). Plural nozzles are grouped with one well, forming 4 wells, each having 4 nozzles associated therewith, as shown in Figure 27C (line c in Figure 27A). Figure 27D shows a sectional view of the nozzle array (line d in Figure 27A).

Applications

The herein described micro and nano nozzles may be used for various applications. For example, any known or future developed process that may employ "writing" techniques to deposit codes, conductors, patterns, devices, or any other material. These micro and nano nozzles may be used to build the soon to be ubiquitous nano-devices including electronic, mechanical, nano-fluidic, and many more.

Lithography

Any of the herein described nozzle systems may readily be employed for nanolithography. Referring now to Figures 28A-B, an embodiment of a nanolithography process is shown. A nozzle device 400 having a tip 410, e.g., manufactured according to one of the techniques described herein, is operably connected to a control system 420. A substrate 430 is shown onto which lithographic material 440 is deposited. The lithographic material is contained in the well of the nozzle (as described hereinabove), and is deposited under operation of the control system. For example, material may be deposited upon application of a field across electrodes formed as described above. Further, a pressure system may apply pressure to eject material 440 from the well of the nozzle device 400 through the tip 410. With a suitable X-Y motion controller (or in certain embodiments an X-Y-Z motion controller or a R, theta motion controller), any

desired lithographic pattern 440 may be applied to the substrate 430.

Referring now to Figures 29A-B, another embodiment of a nanolithography process is shown. A nozzle array 500 includes plural nozzle tips 510, manufactured as described herein, is operably connected to a control system 520. A substrate 530 is shown onto which plural lithographic material traces 540 are deposited. Note that while the traces 540 are shown as various types of dashed lines, it should be understood that this is to distinguish the various traces. These lines may be deposited as solid lines or in various patterns. The lithographic material is contained in the well of the nozzle, and is deposited under operation of the control system.

Both the system of Figures 28A-B and the system of Figures 29A-B may be employed to deposit various materials, such as ink, conductor traces, acids (e.g., as in etching operations), other materials to be nano-deposited on a substrate, and any combination comprising at least one of the foregoing. Note that the lithographic material may comprise microparticles or, in certain preferred embodiments, nanoparticles, for example, in a suitable suspension or solution.

Protein Sequencing

In certain embodiments of using the herein micro and nano nozzles, fast protein and DNA sequencing is attainable. The development of high-throughput DNA sequencers in the 90's have helped launched the genomic revolution of the 21st century. Almost on a monthly basis, one research group or another is announcing the complete sequencing of a biologically important organism. This has allowed researchers to cross reference species, finding shared and/or similar genes, and allowing the knowledge of molecular biologists in all the various fields to come together in a meaningful way.

However, current techniques in DNA sequencing are far too tedious, tying up the valuable time of researchers. Even the fastest, most advanced DNA sequencers can at most process a few hundred thousand base pairs a day. The Human Genome Project took over 10 years to complete, indicating that current DNA sequencing technology still has a long way to go before it can be used as a diagnostic tool.

Using the herein nano-nozzles, a DNA sequencing method is presented that may sequence the entire Human Genome in a matter of minutes. Realizing and optimizing this technology opens new vistas for human endeavors, and enables practical applications that are nearly limitless. Culturing bacteria would be a thing of the past. Whenever faced with an unknown organism, not only could its exact species be determined immediately, but also its entire genotype, including new mutations or signs of genetic engineering. This process is based on utilization of the nanoscale nozzles and detection of ultra small and ultra fast signals. This may lead to the development of the ultimate sensor, not only for DNA, and RNA, but also to sequence denatured proteins (amino acid sequence of polypeptides).

Current DNA sequencing technology is most often based on electrophoresis and polymer chain reaction (PCR). PCR is used to create varying lengths of the DNA in question, which is then subjected to electrophoresis to resolve the size differences between the DNA fragments. However, this technique faces several bottlenecks. First, although PCR is useful in amplifying the amount of DNA material, it is time consuming, requires numerous reagents, including the use of an appropriate primer. Second, electrophoresis speed is dependent on the applied voltage. But the applied voltage cannot be further increased unless heat dissipation is similarly increased. Also, electrophoresis

gel is only capable of resolving a small dynamic range (<500bp). This requires splitting an organism's genome apart for sequencing and then re-assembling the pieces.

Instead of relying on electrophoresis to resolve the DNA sequence, the proposed sequencing technology is based on nano-electronics. Referring now to Figure 30, the basic principle is described, wherein a DNA chain (or other protein) 600 is passed underneath four nano-sized nozzles 610 (or arrays of nozzles, e.g., as shown in Figure 31). The four nozzles 610 are filled with adenine, cytosine, guanine, and thymine molecules respectively. Due to the complementary structures of adenine and thymine, and of guanine and cytosine, a hybridization event between nucleotides on the DNA chain and the nucleotides in the nozzle will occur when the correct pairs come into contact. This hybridization results in a lower energy state and charge transfer, which can be detected via an ammeter. This is because the conductivity between the nozzles and the electrode ground plate will be affected, thereby altering the current between the nozzle and the ground plate.

One important factor of this method is obtaining a sufficient signal to noise ratio. The system is preferably gated and synchronized such that the ammeter will only detect a signal when a nucleotide is directly below a nozzle. The bias applied may be positive, negative, or even alternating, as to maximize the change in conductivity. Cooling may be desirable to reduce the thermal noise. Alternatively, each DNA or protein strand may be passed under several arrays of nozzles, thereby averaging out the noise. Figure 31 shows an exemplary array setup, e.g., that may average out noise and increase SNR. These features will help in assuring an excellent SNR.

However, if we assume a 10 picoamp current change under one applied volt, and

10 nanoseconds for detection, the signal is orders of magnitude larger than the thermal noise, even at room temperature. The sequencing speed would be enormous. Allowing 30 nanoseconds to move a nozzle from one nucleotide to the next (a speed of about 1 cm/sec), it would take only 40 nanoseconds to sequence one base pair, which is equivalent to1.5 Billion base pairs a minute.

The above described DNA sequencing is enabled by creating a nozzle having tip dimensions on the order of about 5 Angstroms, for example, utilizing the above referenced and described nozzle manufacturing methods.

Referring now to Figure 32, an embodiment of an ultra-fast DNA sequencing system 700 is shown. The sequencing system uses a nozzle array 710, as described herein. Further, the sequencing system uses a nano-metrology system 720 to precisely guide denatured DNA strands across the individual nozzles in the nozzle array.

Referring now to Figure 33, a schematic of major components of the ultra-fast DNA sequencing system 700 are shown. A nano-nozzle set array platform 730 upon an N-channel specimen array platform 728 is operably connected to a detector array 732 associated with a processor 734, generally for determining instances of hybridization events induced by the biases applied via a gated bias array control 736. The DNA specimens are maintained and displaced in relation to the array with a stepped motion control 738, which is also operably connected to the processor 734. The array platform 728 is movable at a velocity of about 0.1 to about 1 cm/s. Preferably, as shown, the motion is in a stepped manner, as described herein. The sequencing results are shown on a sequence display 740.

The stepped motion is important in preferred embodiments, as the motion and number of steps helps maintain knowledge of position on the ssDNA, and ultimately the position of hybridization events. The stepped motion may be from about 5% to about 100% of the nozzle opening dimension, preferably about 10% to about 25% of the nozzle opening dimension.

The gating is also important in preferred embodiments, as extremely synchronized current measurements, bias, motion steps, or other excitations are crucial to ultra-fast real time DNA sequencing.

Referring now to Figure 34, a top view of the ultra-fast DNA sequencing system 700 is shown. The DNA specimens are denatured and maintained within channels 744.

Referring now to Figures 35A-B (wherein Figure 35A is a section along line A-A of Figure 34), each channel 744 includes biasing systems for applying voltages across the DNA samples. As described in more detail herein, hybridization events induce measurable current variations across each of the nanonozzles within the nanonozzle set array platform. Preferably, the alignment between the nanonozzles and the channels is extremely precise.

Referring now to Figure 36, detailed section views of the sequencing process are shown. The nanonozzle set array platform includes nanonozzles with wells, or nucleotide reservoirs, of A,C,T and G molecules. The strands are moved along the channel and molecules from the nucleotide reservoirs interact with the molecules of the strand through the nozzle. These molecules hybridize with one other molecule (e.g., A with T, C with G) as is known in the art.

Referring now to Figure 37, detailed views of hybridization events are shown. Only a hybridization event at the nanonozzle results in a measurable current pulse.

Referring now to Figure 38, it is shown that, of all possible 16 combinations of A,T,G and C, only four produce current pulses upon a hybridization event.

As mentioned above, only a hybridization event produces a measurable (nanoseconds) current pulse at the nozzle. For proper operation, the following principles apply.

- All excitation sources, detectors and stepped motion are synchronized.
- Synchronized steps should be a fraction of the nozzle opening size (e.g., on the order of 5 nanometers).
- Nozzle locations should be known with nanometer or sub-nanometer precision in relation to a known reference position.
- Nanometer alignment is very important to optimal operation.
- Vibrations and other agitations should be minimized.
- A system is needed to measure very low amplitude nanosecond pulses.
- For continuous real time measurement of millions, or even hundreds of millions, of base pairs, a wide dynamic range sub-nanometer stepper is preferred.
- To calibrate the system, it is desirable to use known samples.

Referring now to Figure 39, a reference position and precision nanometer metrology system is shown. A reference position probe (RPP), e.g., formed of platinum or other suitable material, or in the form of a nano-light guide, or other excitation means, is included in the nanonozzle array set. The positions of each nanonozzle relative the RPP is shown. This probe provides a spatial zero when sequencing commences.

Referring now to Figure 40, the stepped motion of ssDNA is shown relative to a known position of the RPP.

To assist the denaturing in conjunction with the precise stepwise motion, the DNA strand can be straightened bay various methods. In one embodiment, electrostatic fields may be used to attract the negatively charged strands. In another embodiment, a magnetically attractive bead may be applied to an end of the DNA strand, and the strand pulled with magnetic force. In a further embodiment, viscosity optimization may be employed, such that while dragging the strand through a liquid proximate or in the channel, it will straighten upon optimal dragging velocity and fluid viscosity conditions. Further, hydrophilicity may be used, e.g., by suitable material treatment at or in the nozzles and channel walls, to attract nucleotides. In other embodiment, hydrophobicity may be used, e.g., by suitable material at or in the nozzles and channel walls, to maintain the fluid within the channel.

Thus, as shown and described, the herein system including nano-nozzles and nano-nozzle arrays are very well suited for ultra fast real time DNA sequencing operations.

Chemical Synthesis and Analysis

As is apparent to those skilled in the art of nano-chemistry or micro-chemistry, the herein described nozzles may readily be utilized in systems for combining various materials for chemical reaction, or chemical detection and analysis. For example, the nozzle may dispense a chemical "A" that interacts in a known manner with a chemical "B" provided in sufficiently close range with the nozzle. As with the above described hybridization current changes, a measurable event occurs when A interacts with B. This

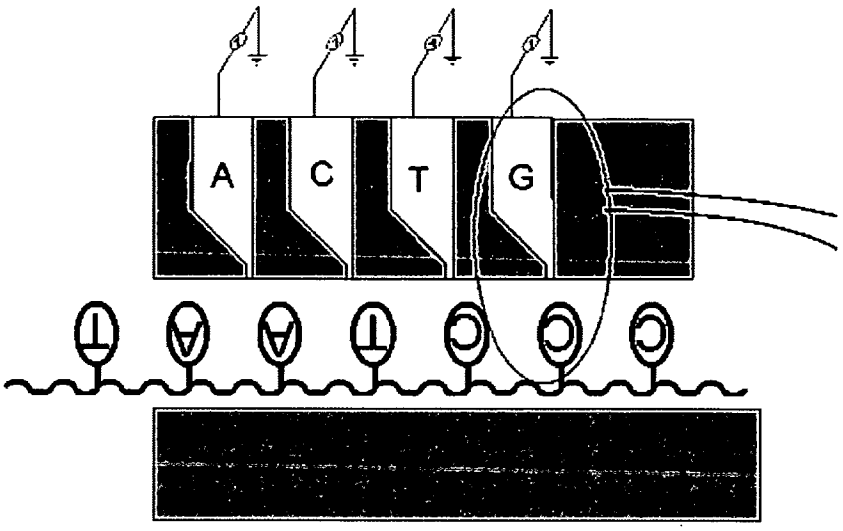
measurement may be, e.g., a current change, inelastic tunneling conduction, or a wavelength shift.

Further, a probe may be incorporated in the nozzle system (preferably manufactured to known dimensional relationship with the array) to measure current change, inelastic tunneling conduction, or a wavelength shift.

Additionally, DNA synthesis may be enabled by using nano-nozzle arrays of the present invention.

While preferred embodiments have been shown and described, various modifications and substitutions may be made thereto without departing from the spirit and scope of the invention. Accordingly, it is to be understood that the present invention has been described by way of illustrations and not limitation.

This disclosure contains inventions that may be considered to be individual inventions or improvements to previous inventions by Dr. Faris embodied in a patent application entitled "Micro-Nozzle, Nano-Nozzle, Manufacturing Methods Therefor, Applications Therefore, Including Nanolithography and Ultra Fast Real Time DNA Sequencing", covered in U.S. Patent Application No. 10/775,999 and PCT Application No. PCT/US04/03770 (publication number WO2004/071948), filed on February 10, 2004, based on the priority date of February 10, 2003. A copy of this referenced application is included herewith and its contents are incorporated herein by referece.



The ideal DNA sequencing device will follow the following parameters:

Rule 1) In order achieve high spatial resolution, a probe is needed that is spatially smaller than the desired resolution. That is, to resolve a subject having a topography of X spatial "roughness", we need a probe with spatial dimensions less than the shortest distance of the subject's molecular spacing. Subject DNA strands generally have nucleotide spacing of ~ 0.5 nm, therefore to resolve this, the probe tip should be < 0.5 nm. This is possible using the methods described in the above-referenced application Faris U.S. Patent Application No. 10/775,999 et seq.

Rule 2) Knife Analogy - to measure a DNA strand, while the probe dimension along the direction of analysis must be smaller than the shortest distance of the subject's molecular spacing, the dimension of the probe perpendicular (or otherwise) to the direction of analysis should be much larger, similar to the comparison of a knife edge to the blade length. That is, the "knife edge" must be smaller than the resolution of spatial size, the blade length should be comparatively large so that the "knife edge" of the measurement probe always lands perpendicular to the subject strand, and landing error is minimized or eliminated. This is in contrast to the pin probe, where landing error is high.

Rule 3) We can have many different types of probes.

3.1 nucleotide filled well (see Faris U.S. Patent Application No. 10/775,999 et seq. referenced above)

3.2 Solid State nucleotide[1]
3.3 Metal conductor[2]
3.4 X-rays
3.5 Electron beam
3.6 Electron beam with inelastic tunneling emission
3.7 Light pipe
3.8 Metal plus known nucleotide stand, preferably same species[3]
3.9 Ion beam

Rule 4) Noise reduction sub-system
4.1 Gating program – allows one to sequence different events/subjects with different programs
4.2 redundancy

Rule 5) stretching sub-system

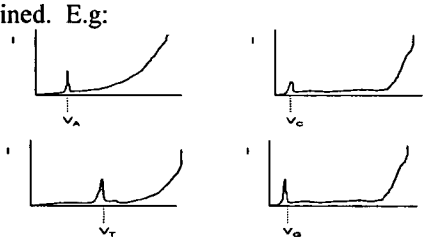
Rule 6) high resolution motion, such as stepping. For ideal high speed high resolution analysis, the step should be less than 0.5 nanometers, the distance between nucleotides.

---

[1] The Solid State Nucleotide may be manufactured on thin films. These films may be formed in the nozzle wells, e.g., by layering during the manufacturing process prior to slicing. Preferably, these SSN have a single molecule thickness at the probe tip, so that the resolution rule 1 is maintained.

[2] The metal conductor is based on having the nozzle filled or layered with metal conductor material. The metal may be platinum, gold, or other suitable metal.

Stimuli (e.g., a voltage) is applied across the subject nucleotide within the subject strand, and a characteristic I vs. V curve is obtained. E.g:



Gated application of stimuli
Resonant capacitance – we may use RF excitation
The "knife" analogy also serves to lower the resistance in this embodiment
May be used in 4 probe system –

Various embodiments are possible:
1) voltage only
2) voltage plus light (AND gate)
3) synchronization – with gating, pulsed voltage, light, current gate – leads to substantial noise reduction
    a. step
    b. apply voltage + light (AND gate)
    c. apply current gate (measure with ammeter)
4) kT small if low temperature operations – T between 4 and 100 K

[3] A single strand/single species nucleotide strand is provided. It is stretched and attached to a metal "knife edge" as described above. It may be attached by various nano- or micro- manipulation means. For example, magnetic "beads" may be attached at opposing ends of the known strand to facilitate manipulation.
This single-strand, single-species chain attached at the probe enhances the resonance activity and capabilities of measuring a hybridization event.

What is Claimed is:

1. A nozzle structure comprising:

a monolithic body having an array of nozzles, the nozzles having sectional openings having heights of about 100 nm or less,

the nozzles associated with a well structure.

2. The nozzle structure as in claim 1, wherein the nozzles have sectional openings having heights of about 50 nm or less.

3. The nozzle structure as in claim 1, wherein the nozzles have sectional openings having heights of about 20 nm or less.

4. A nozzle structure comprising:

a monolithic body having an array of nozzles, the nozzles having sectional openings having heights of about 100 nm or less,

each nozzle being associated with a well structure.

5. The nozzle structure as in claim 4, wherein the nozzles have sectional openings having heights of about 50 nm or less.

6. The nozzle structure as in claim 4, wherein the nozzles have sectional openings having heights of about 20 nm or less.

7. A method of producing a nozzle comprising:

processing a well on a layer supported by a substrate, the wells having a recessed region and at least one sloped wall, the layer having a plateau region adjacent the well;

processing an etch removable layer at least at the plateau region;

removing the layer;

repeating the above steps at least one time to provide a plurality of layers each having a well therein;

aligning and stacking the layers;

cutting the stack of device layers substantially at the plateau regions of the well to expose a cut edge; and

etching from the cut edge at least a portion of the etch removable layer at the plateau to create a nozzle tip.

8. The method as in claim 7, wherein the thickness of the etch removable layer defines a thickness dimension of the nozzle tip.

9. The method as in claim 7 further comprising:

grinding, polishing, or otherwise removing material from the cut edge of the stack to minimize the length of the plateau area prior to etching.

10. The method as in claim 7 wherein the well is substantially symmetrical, further comprising slicing through the recessed region of the well thereby providing a pair of structures to be cut in the area of the plateau.

11. The method according to claim 7 further comprising, prior to removing the layer, filling the recessed region of the well with a removable material.

12. The method as in claim 7, wherein a thickness of the etch removable layer defines a height dimension of the nozzle opening.

13. The method as in claim 12, wherein the thickness of the etch removable layer is about 100 nm or less.

14. The method as in claim 12, wherein the thickness of the etch removable layer is about 50 nm or less.

15. The method as in claim 12, wherein the thickness of the etch removable layer is about 20 nm or less.

16. The method according to claim 7, wherein the nozzle opening is a temporary opening, further comprising

filling the temporary nozzle opening to a defined width with a first material,

filling the region surrounding the first material with a second material, the first material being removable,

removing the first material,

wherein the second material is resistant to the removal of the first material, thereby

creating a nozzle having the defined width, a height defined by the thickness of the etchable material and a length defined by a length of the plateau to the cut line.

17. A method of producing a nozzle comprising:

processing a plurality of wells on a layer of a wafer supported by a substrate, the wells each having a recessed region and at least one sloped wall, the layer having plateau regions adjacent each well;

processing an etch removable layer at least at the plateau regions;

removing the layer;

repeating the above steps at least one time to provide a plurality of layers each having wells therein;

aligning and stacking the layers;

cutting the stack of device layers substantially at the plateau regions of the wells to expose a cut edge; and

etching from the cut edges at least a portion of the etch removable layer at the plateau to create nozzle tips.

18. A method of producing a nozzle comprising:

providing a device layer selectively bonded to a substrate layer with areas of strong bonding and areas of weak bonding;

processing one or more wells in the areas of weak bonding in the device layer wherein the wells have recessed regions and plateau regions;

processing an etch removable layer at least in the plateau regions of the well;

removing the device layer by debonding the strong bond areas and minimally or not at all debonding the weak bond areas;

repeating the above steps at least one time to provide a plurality of device layers having at least one well therein;

aligning the plurality of device layers;

stacking the device layers;

cutting the stack of device layers normal to the surface of the device layers at the plateau regions of the well; and

etching from the cut edge the etch removable layer at the plateau to create a nozzle tip.

19. A method of producing a nozzle comprising:

processing a well on a layer supported by a substrate, the wells having a recessed region and at least one sloped wall, the layer having a plateau region adjacent the well;

processing an etch removable layer at least at the plateau region;

removing the layer;

stacking a cover layer on the layer having the well;

cutting the stack substantially at the plateau region of the well to expose a cut edge; and

etching from the cut edge at least a portion of the etch removable layer at the plateau to create a nozzle tip.

20. A method of producing a nozzle comprising:

processing a well on through multiple known thickness layers, the multiple known thickness layers supported by a substrate, the wells having a recessed region and at least one sloped wall, the layer having a plateau region adjacent the well;

processing an etch removable layer at least at the plateau region;

removing the layer;

stacking a cover layer on the layer having the well;

cutting the stack substantially at the plateau region of the well to expose a cut edge; and

etching from the cut edge at least a portion of the etch removable layer at the plateau to create a nozzle tip,

wherein the known multiple layers provide metrics functionality.

21. A method of detecting a first molecule comprising:

providing a nozzle within a monolithic body having an opening dimension of about 100 nm or less and a nozzle well and an associated electrode;

incorporating a quantity of a second molecule in the nozzle well, the second molecule selected to have known energy state interaction with the first molecule;

providing an electrode associated with the first molecule;

whereby the known energy state is detectable by a potential across the electrodes when the first molecule to be detected and the second molecules are in molecular interaction range.

22. The method as in claim 21, wherein the nozzle has an opening dimension of about 50 nm or less.

23. The method as in claim 21, wherein the nozzle has an opening dimension of about 20 nm or less.

24. A method of sequencing a DNA strand comprising:

providing a nozzle array within a monolithic body, the nozzle array including at least four nozzles, each nozzle having an opening dimension of about 100 nm or less, associated nozzle well and an associated electrode;

providing adenine, cytosine, guanine, and thymine molecules within each of the four nozzle wells;

providing an electrode associated with the DNA strand;

passing a DNA strand under the nozzles; and

detecting across the electrodes hybridization events characterized by a relatively lower energy state when complementary structures of adenine and thymine, and of guanine and cytosine are in molecular interaction range.

25. The method as in claim 24, wherein the nozzle has an opening dimension of about 50 nm or less.

26. The method as in claim 24, wherein the nozzle has an opening dimension of about 20 nm or less.

27. A method of sequencing a DNA strand comprising:

providing a nozzle array within a monolithic body, the nozzle array including at least four nozzles, each nozzle having an opening dimension of about 100 nm or less, associated nozzle well and an associated electrode;

the nozzles filled with adenine, cytosine, guanine, and thymine molecules respectively;

providing an electrode associated with the DNA strand;

providing a reference position probe;

passing a DNA strand under the reference position probe and the nozzles; and

detecting across the electrodes hybridization events characterized by a relatively lower energy state when complementary structures of adenine and thymine, and of guanine and cytosine are in molecular interaction range.

28. The method as in claim 27, wherein the nozzle has an opening dimension of about 50 nm or less.

29. The method as in claim 27, wherein the nozzle has an opening dimension of about 20 nm or less.

30. A method of sequencing a DNA strand comprising:

providing a nozzle array within a monolithic body, the nozzle array including at least four nozzles, each nozzle having an opening dimension of about 100 nm or less,

associated nozzle well and an associated electrode;

the nozzles filled with adenine, cytosine, guanine, and thymine molecules respectively;

providing an electrode associated with the DNA strand;

providing a movable platform for holding the DNA strand;

moving the DNA strand under the nozzles by motion of the movable platform; and

detecting a hybridization event characterized by a relatively lower energy state when complementary structures of adenine and thymine, and of guanine and cytosine are in molecular interaction range.

31. The method as in claim 30, wherein the motion is stepped motion.

32. The method as in claim 31, wherein the stepped motion is in steps of about 0.5 to about 5 nanometer distances.

33. The method as in claim 30, wherein the nozzle has an opening dimension of about 50 nm or less.

34. The method as in claim 30, wherein the nozzle has an opening dimension of about 20 nm or less.

35. A method of nanolithography comprising:

providing a nozzle structure including a monolithic body having an array of nozzles, the nozzles having openings with sectional openings having heights of about 100 nm or less, the nozzles associated with a well structure;

providing lithographic material in the well structure; and

dispensing said lithographic material through said nozzle.

MICRO-NOZZLE, NANO-NOZZLE, MANUFACTURING METHODS THEREFOR, APPLICATIONS THEREFOR

Abstract

A nozzle structure is provided comprising a monolithic body having an array of nozzles. The nozzles having openings with sectional openings having heights of about 100 nm or less. The nozzles are generally associated with one or more well structures.

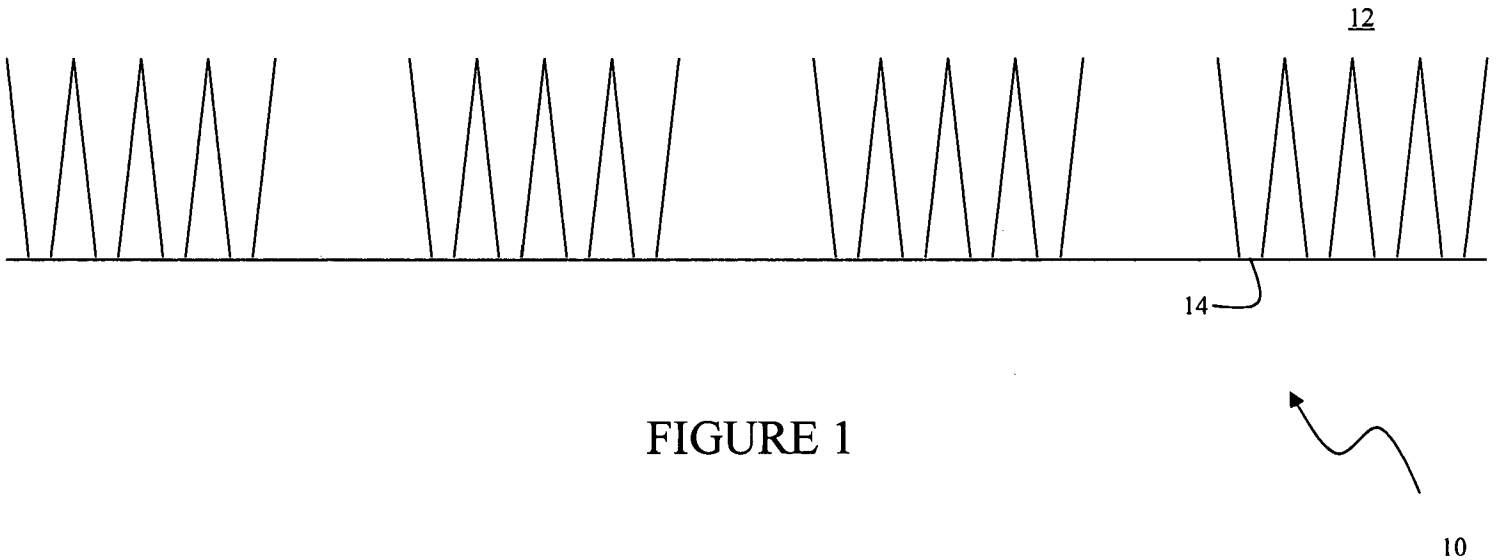


FIGURE 1

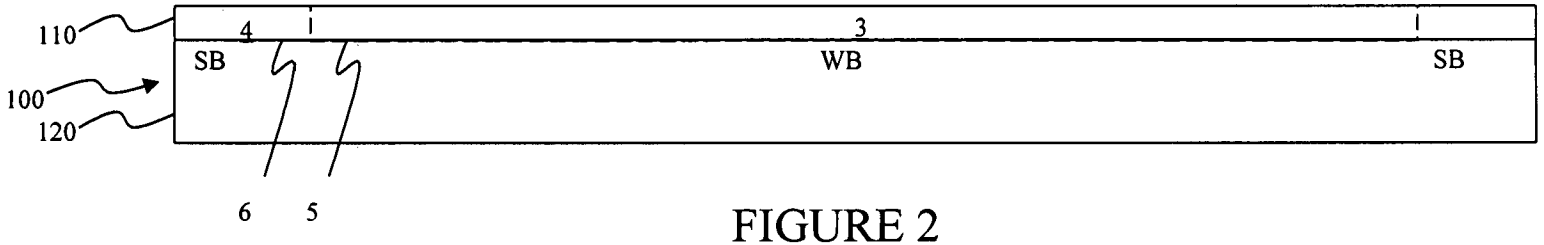


FIGURE 2

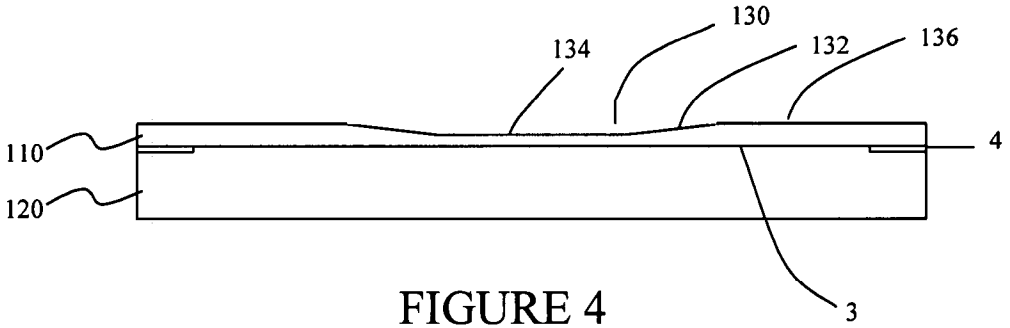


FIGURE 4

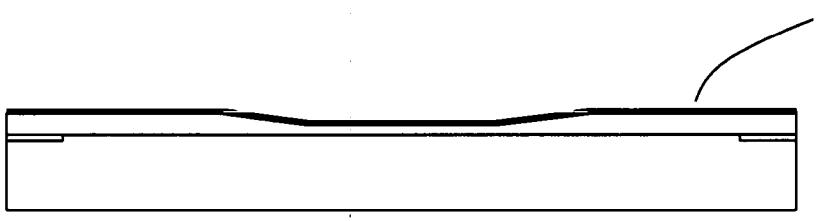


FIGURE 5A

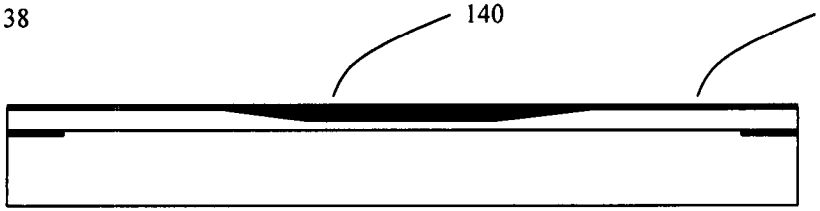


FIGURE 5B

FIGURE 3B

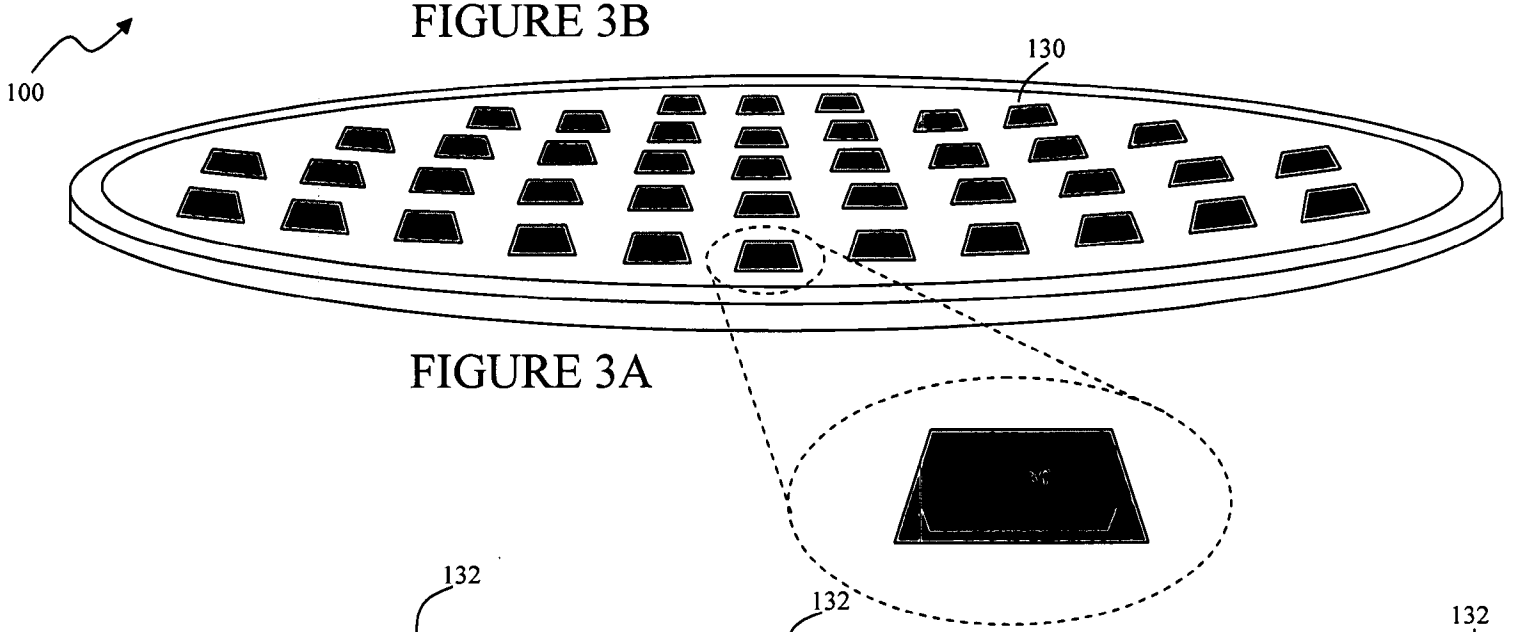


FIGURE 3A

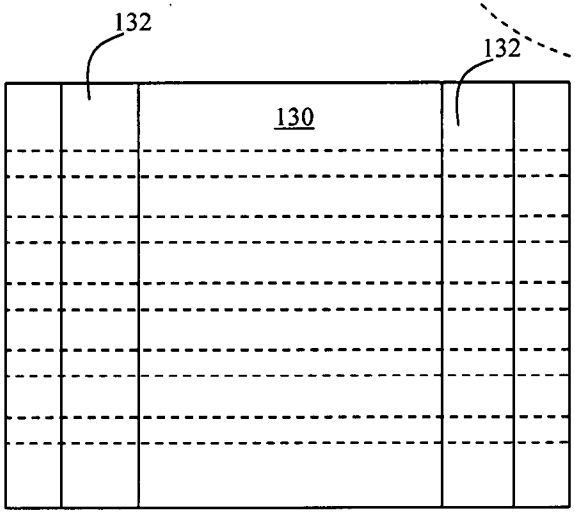


FIGURE 3C

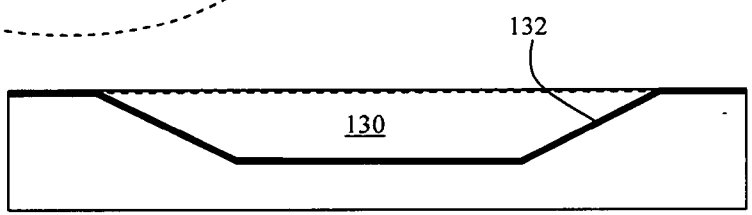


FIGURE 3D

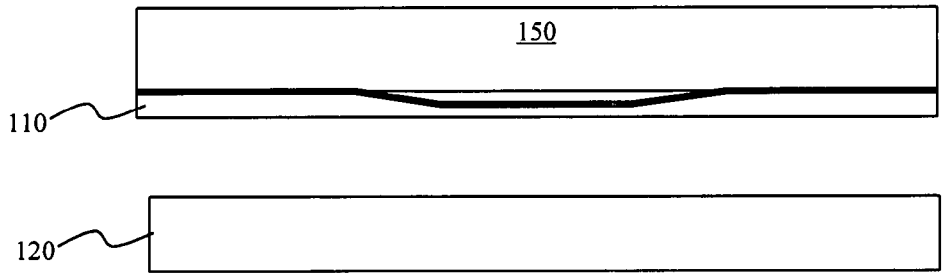


FIGURE 6

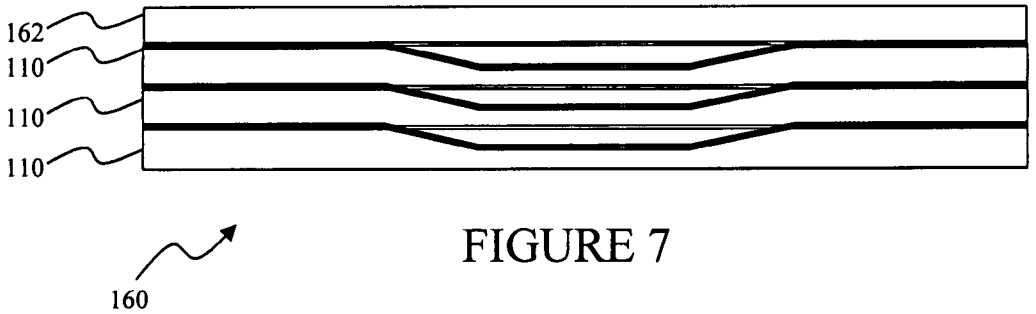


FIGURE 7

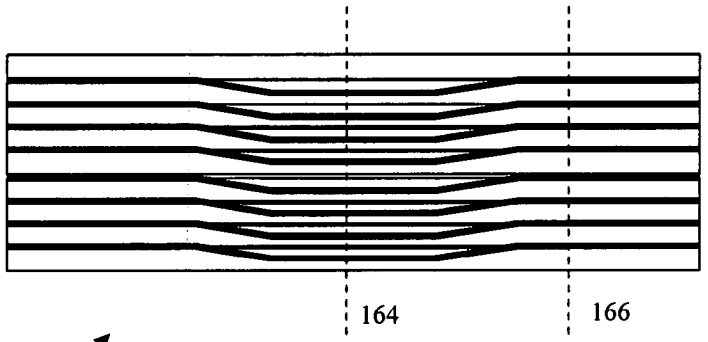


FIGURE 8

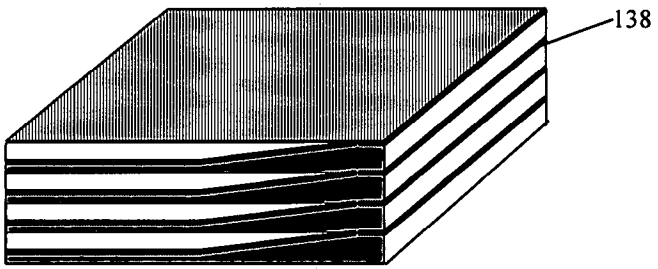


FIGURE 9

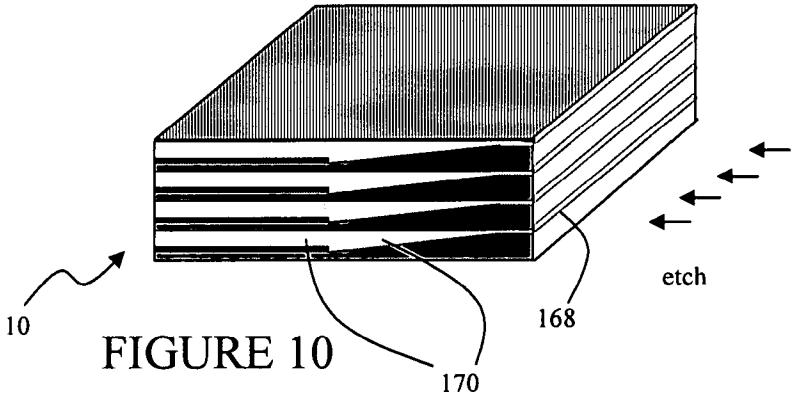


FIGURE 10

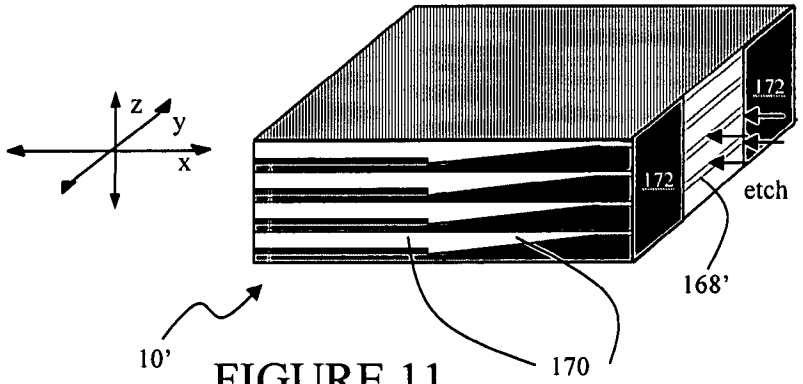


FIGURE 11

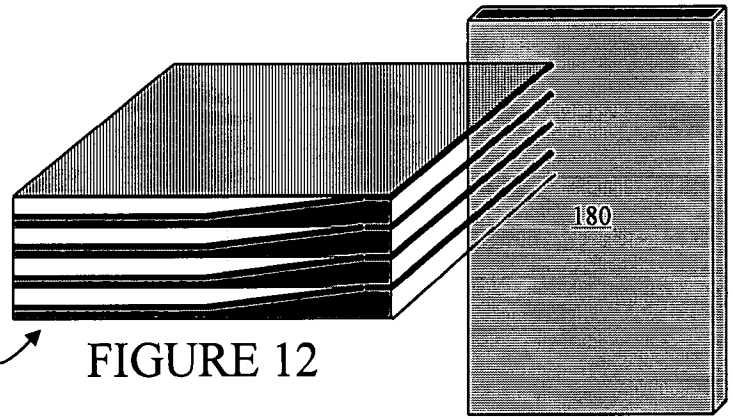


FIGURE 12

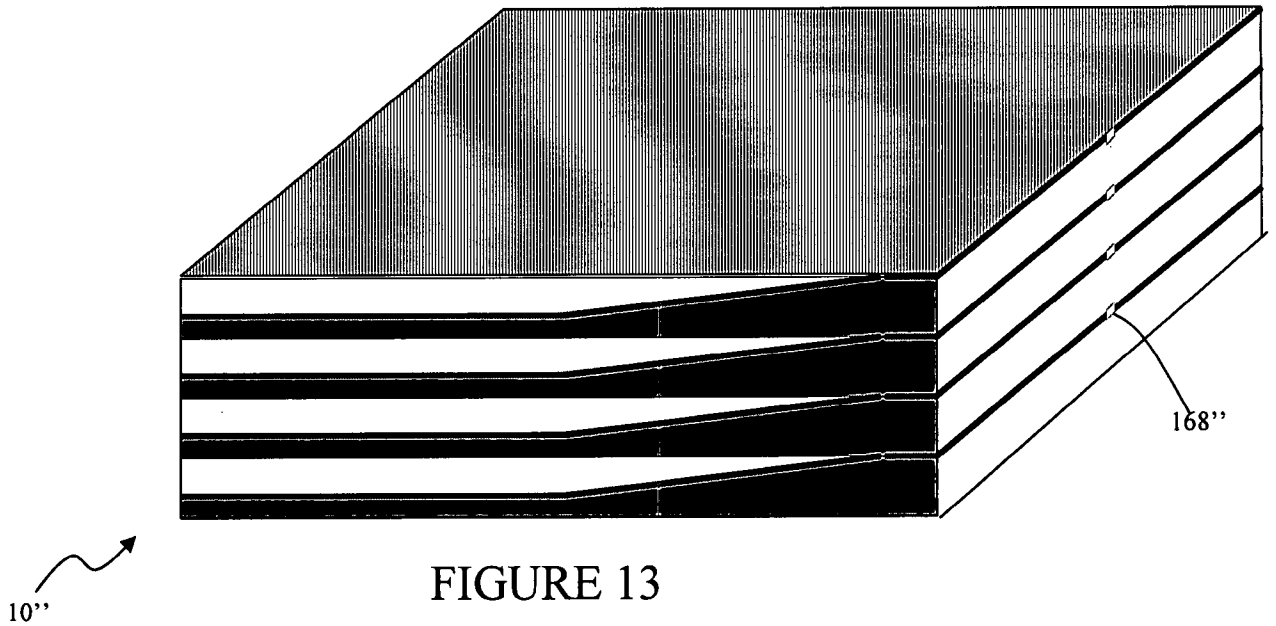


FIGURE 13

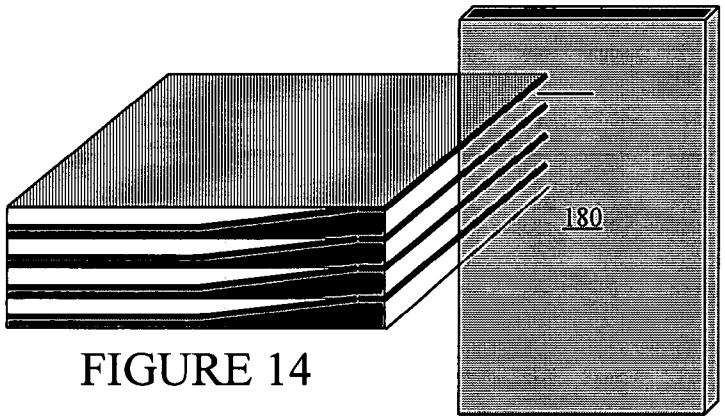


FIGURE 14

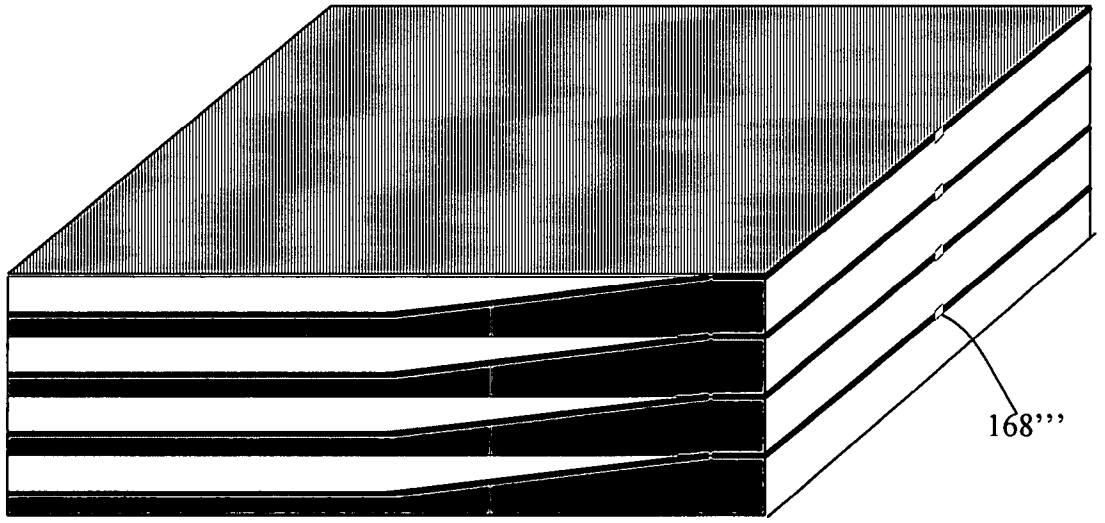


FIGURE 15

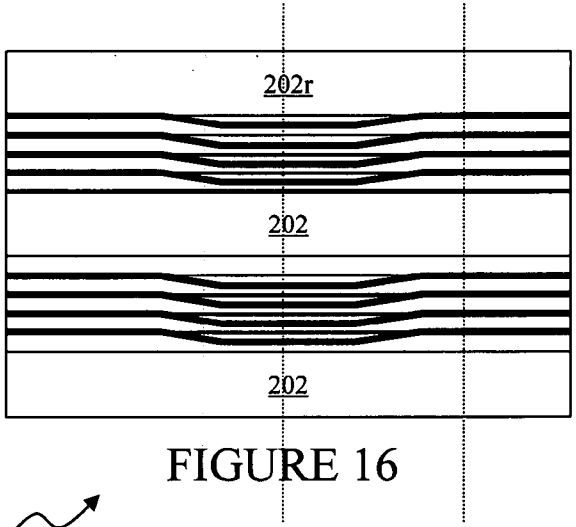


FIGURE 16

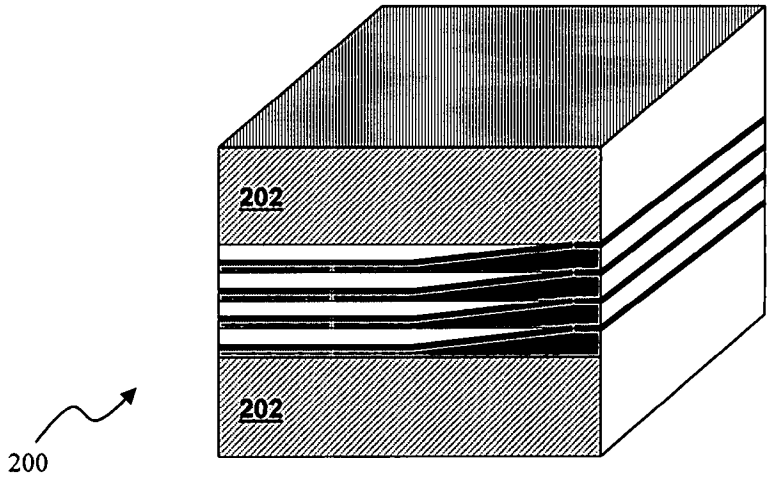


FIGURE 17

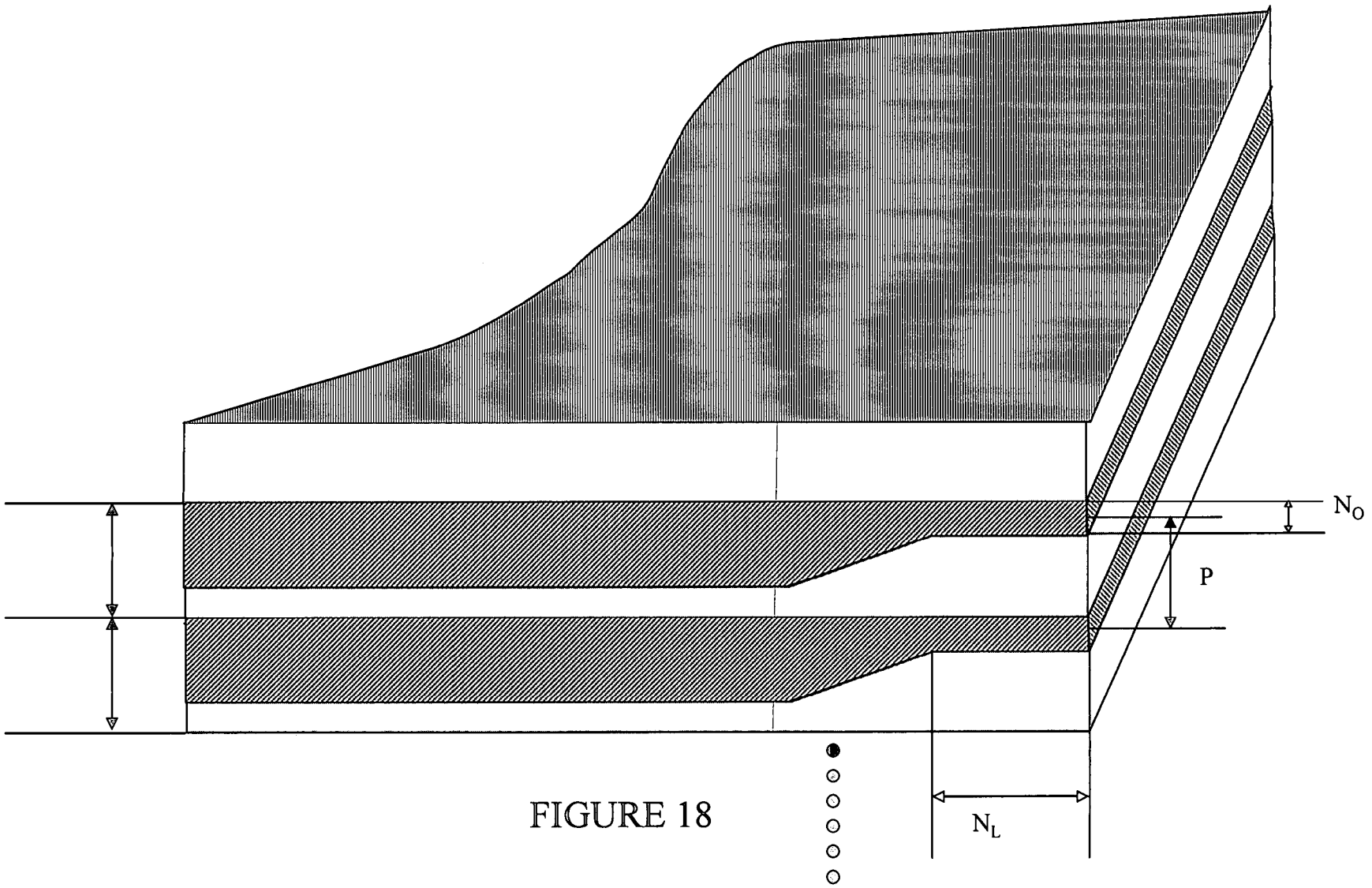


FIGURE 18

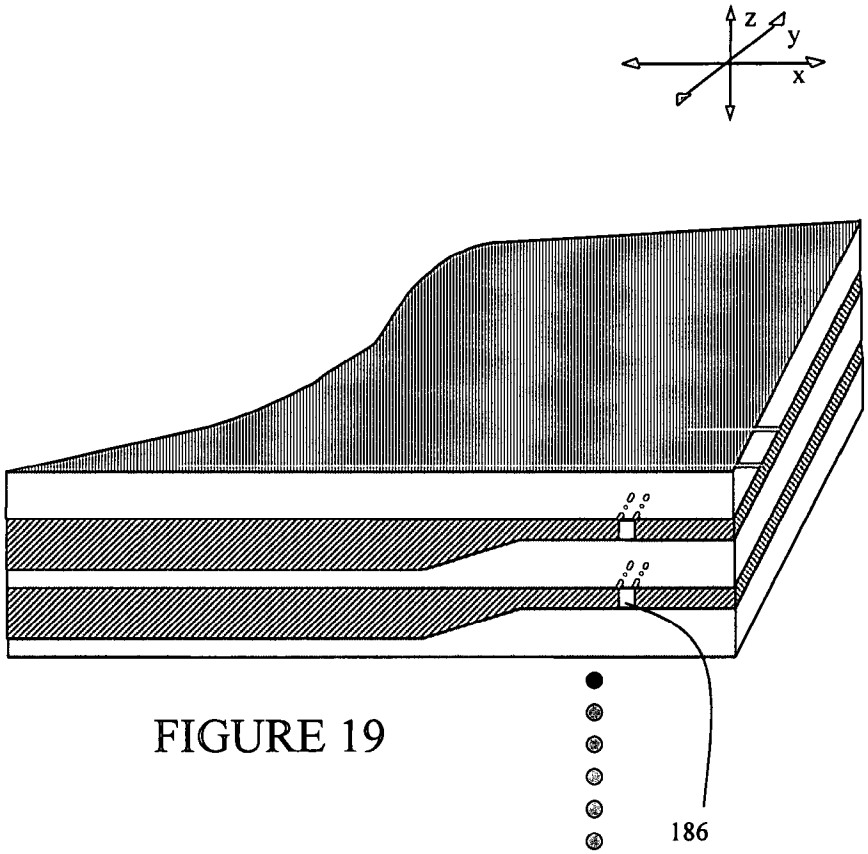


FIGURE 19

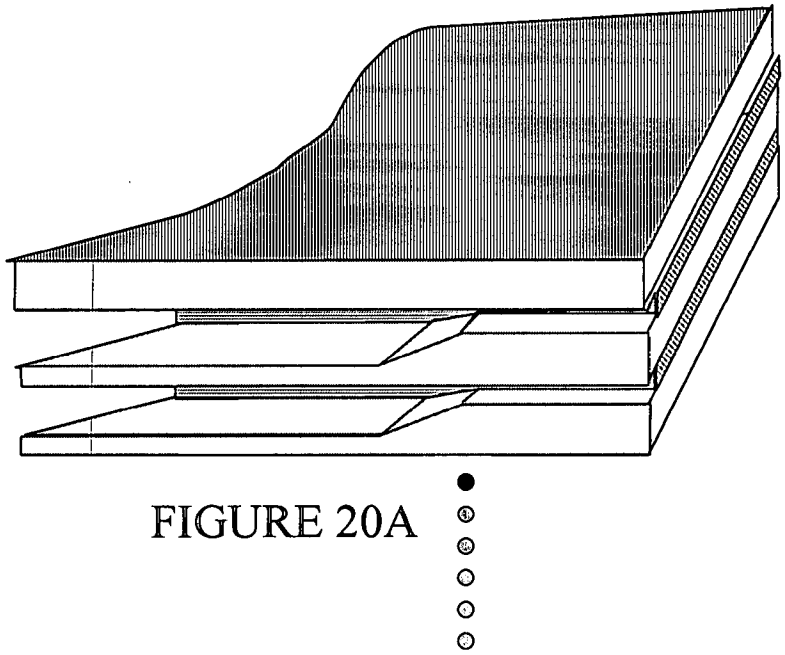


FIGURE 20A

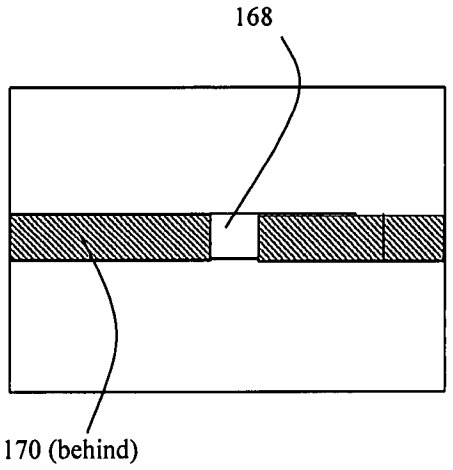


FIGURE 20B

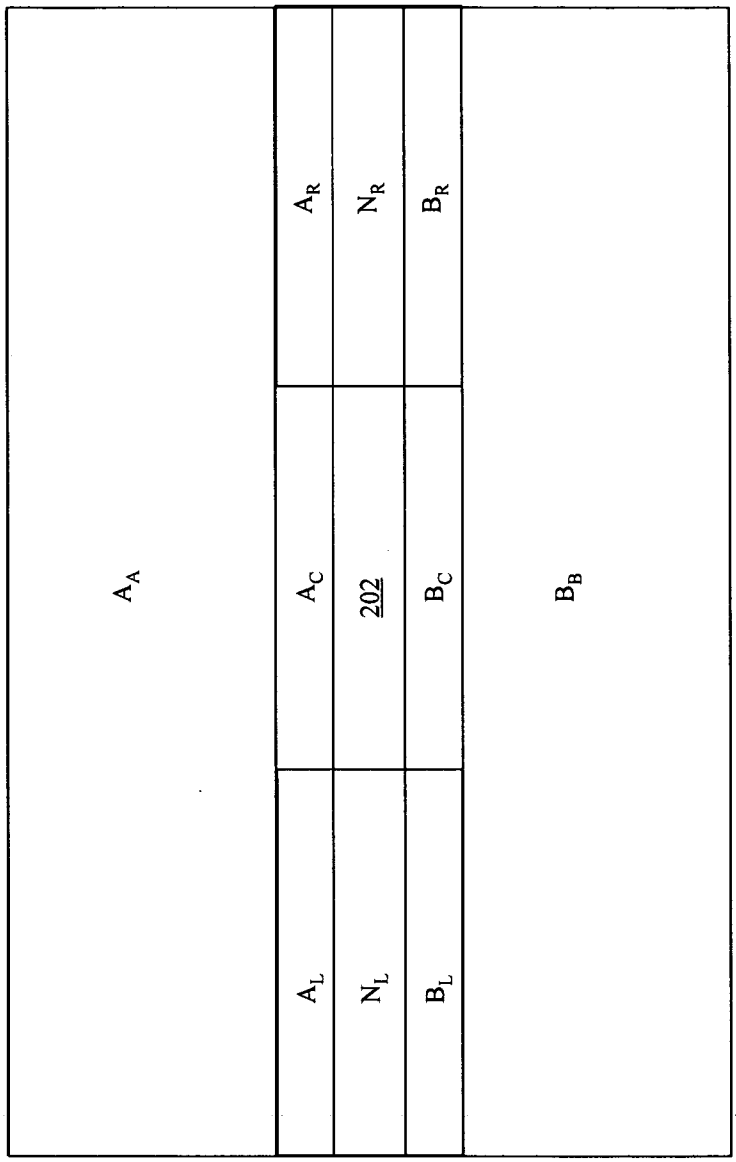


FIGURE 21

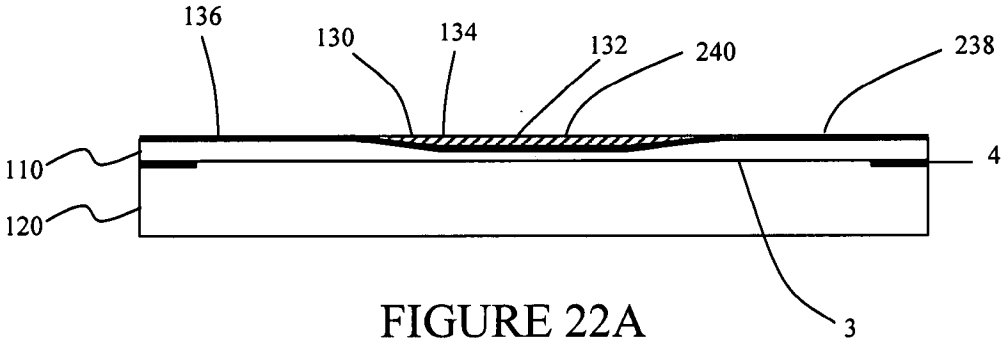


FIGURE 22A

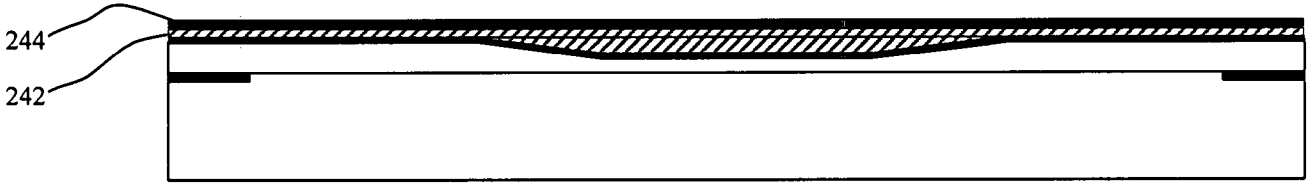


FIGURE 22B

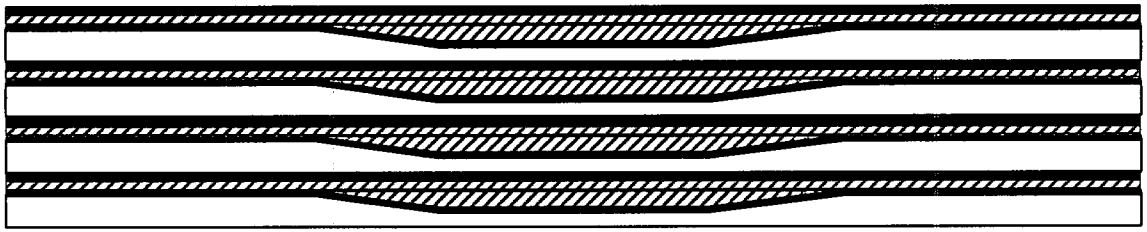


FIGURE 22C

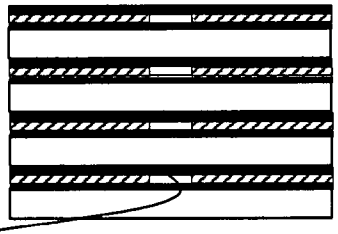


FIGURE 22D

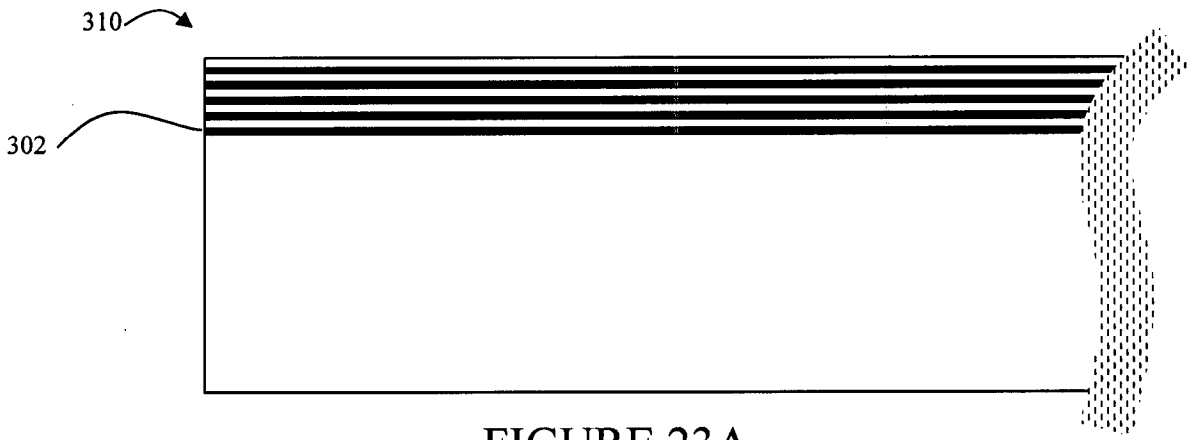


FIGURE 23A

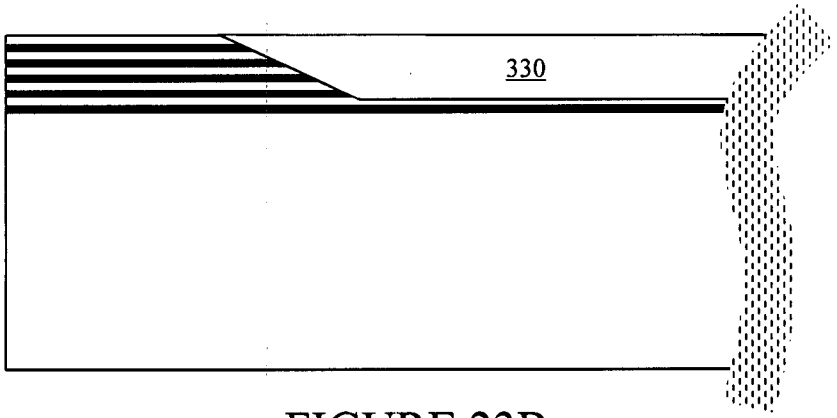


FIGURE 23B

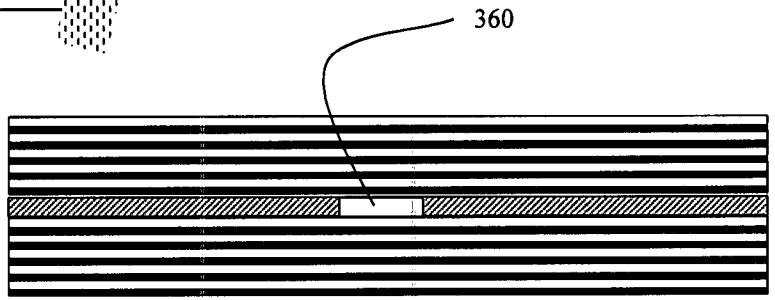


FIGURE 23C

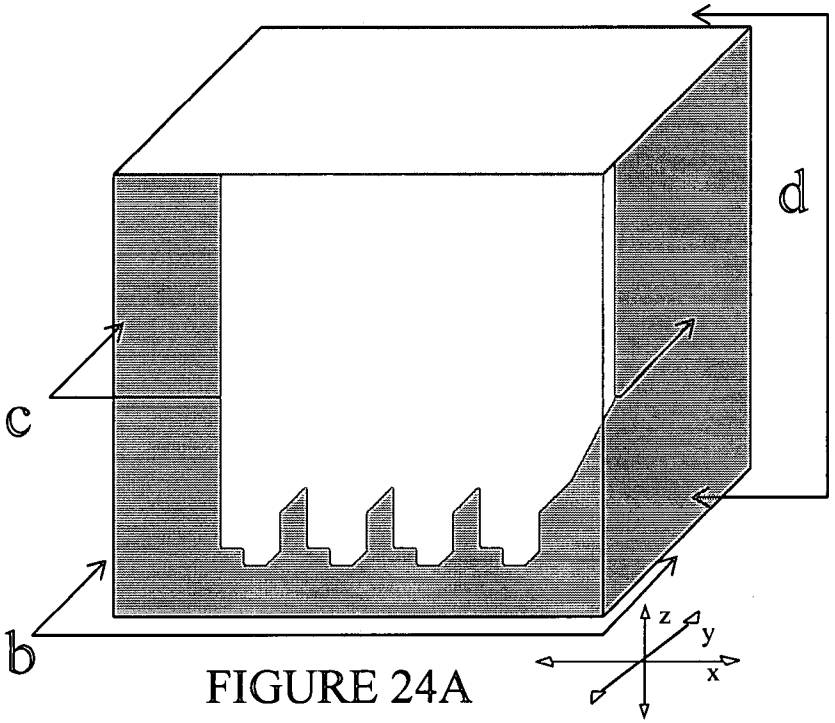


FIGURE 24A

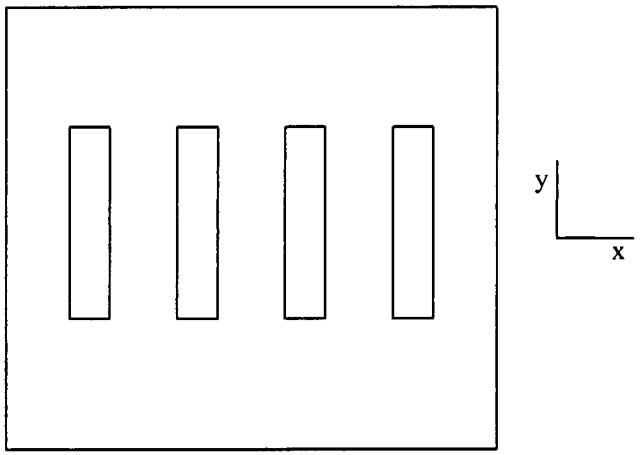


FIGURE 24C

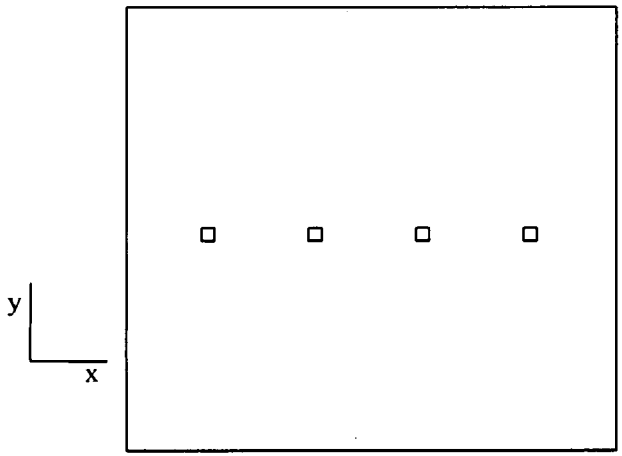


FIGURE 24B

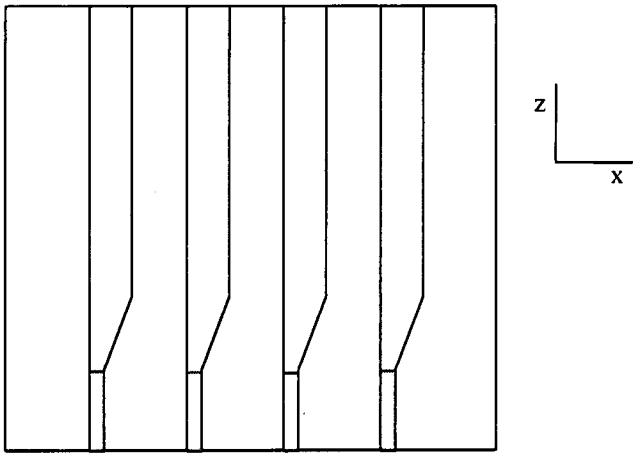


FIGURE 24D

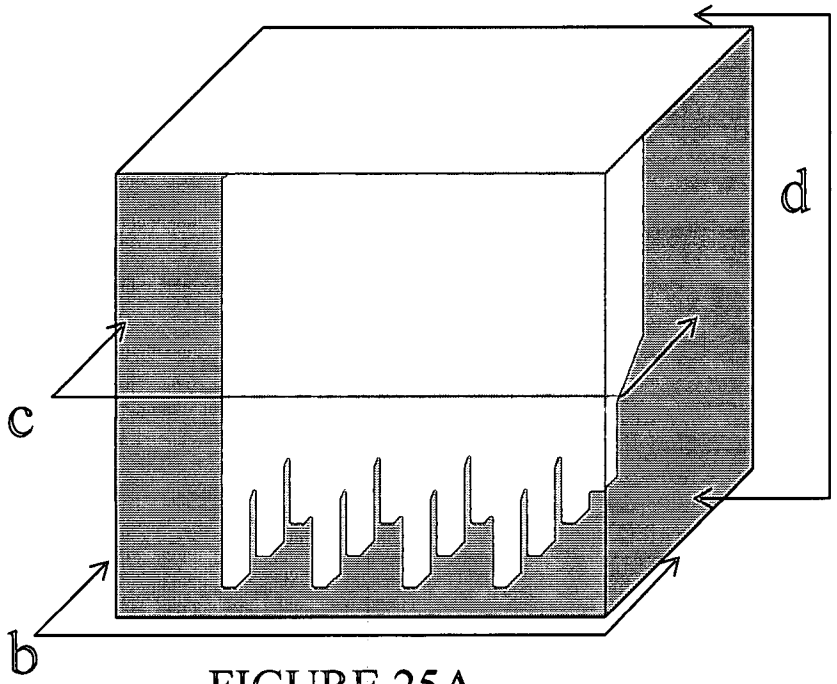


FIGURE 25A

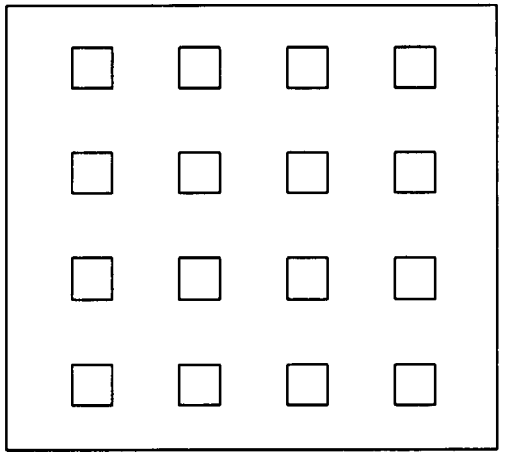


FIGURE 25C

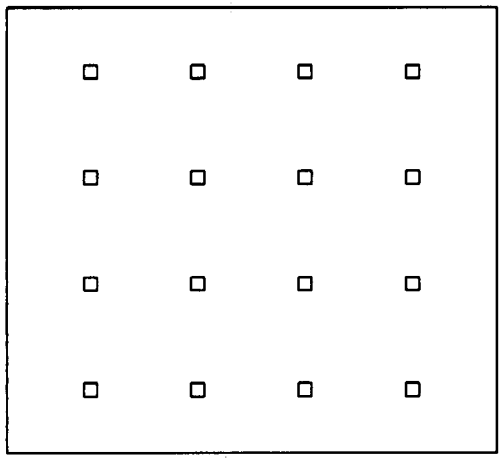


FIGURE 25B

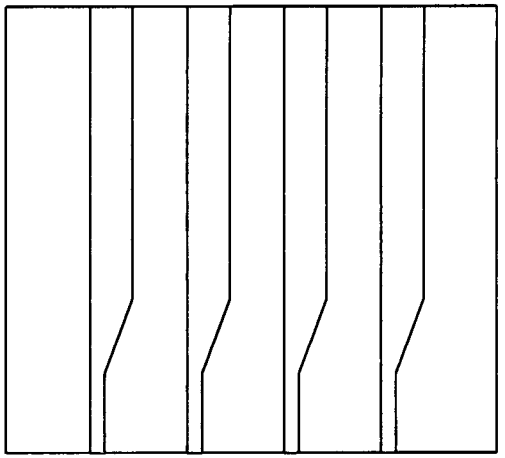


FIGURE 25D

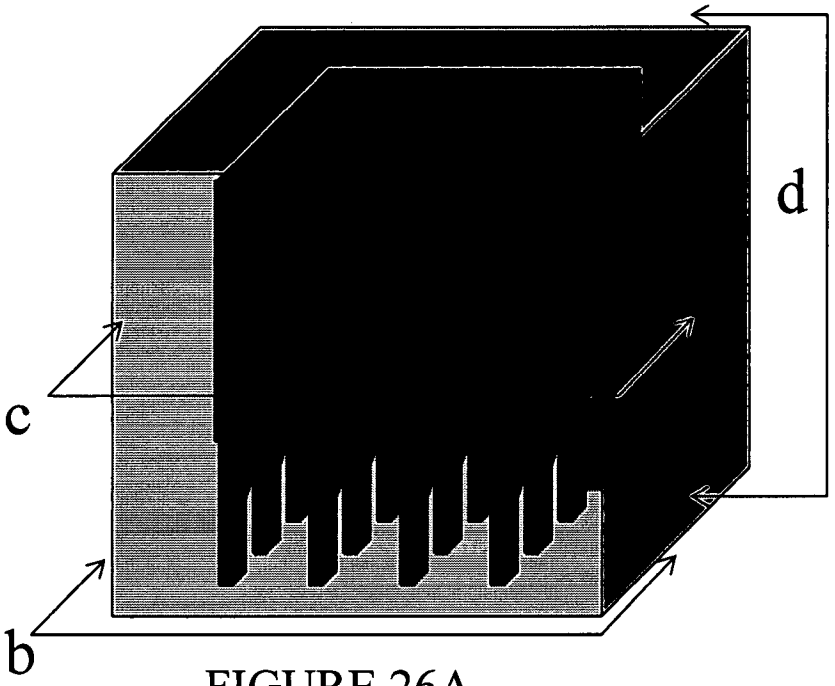


FIGURE 26A

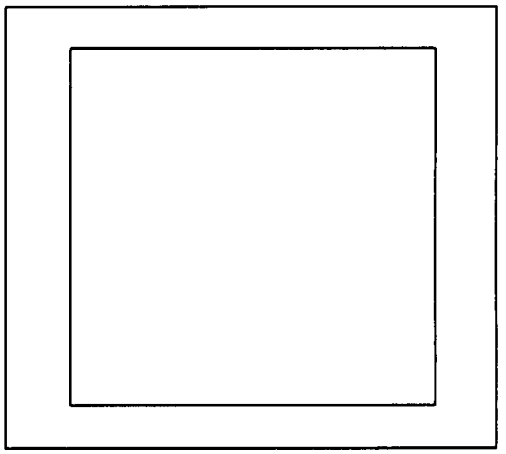


FIGURE 26C

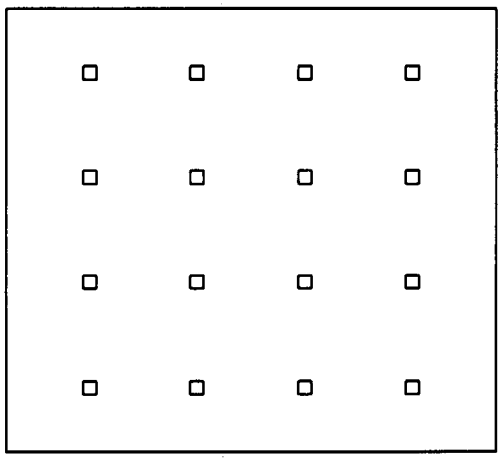


FIGURE 26B

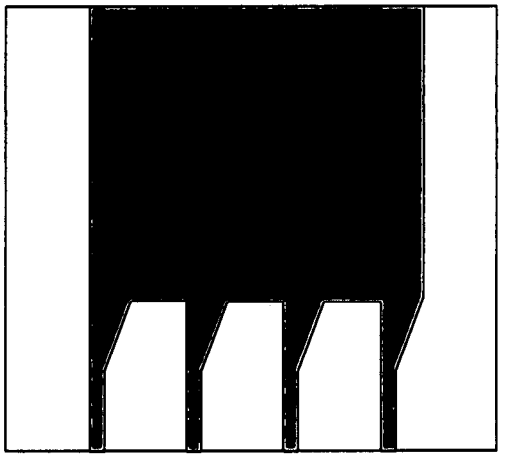


FIGURE 26D

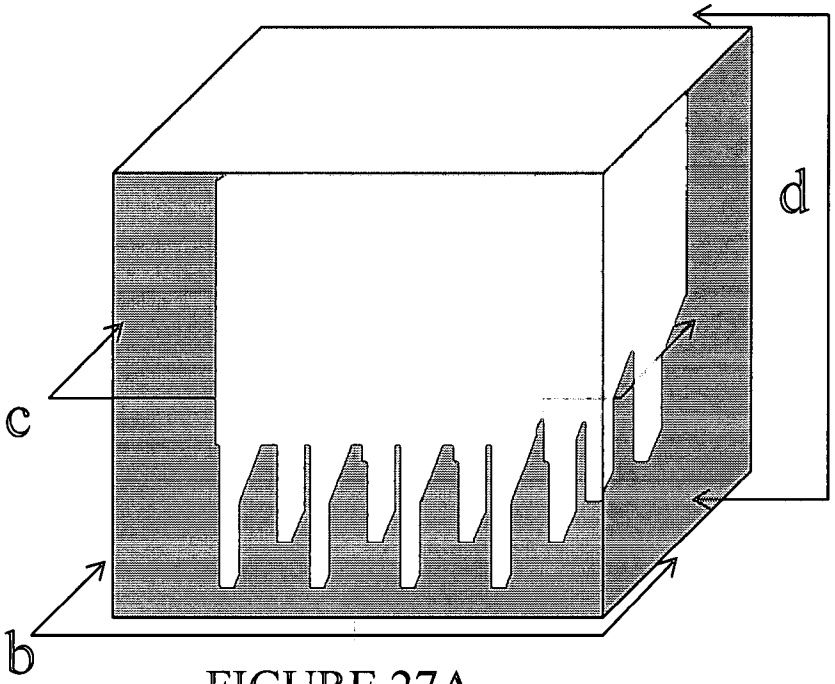


FIGURE 27A

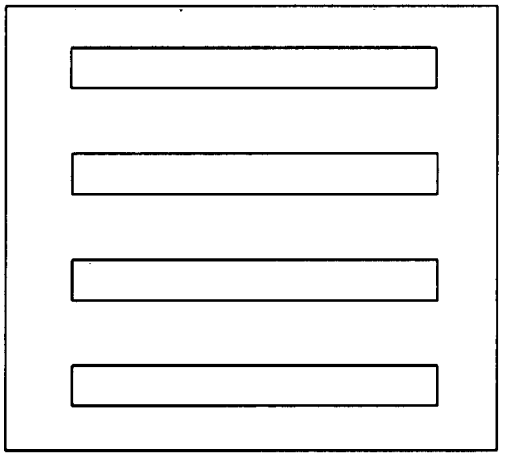


FIGURE 27C

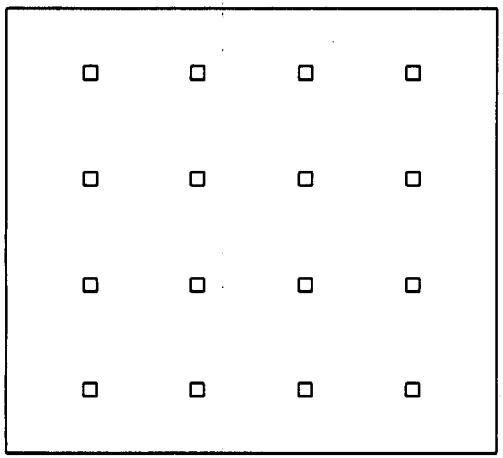


FIGURE 27B

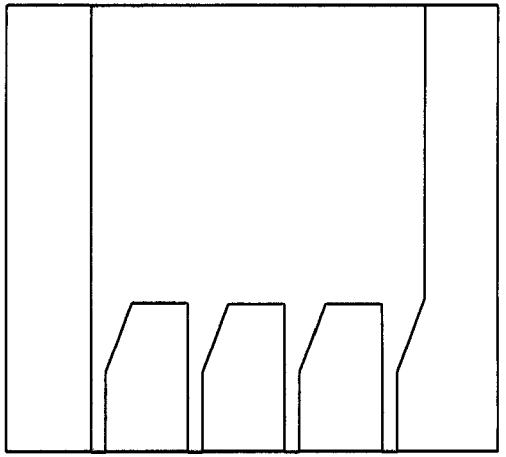


FIGURE 27D

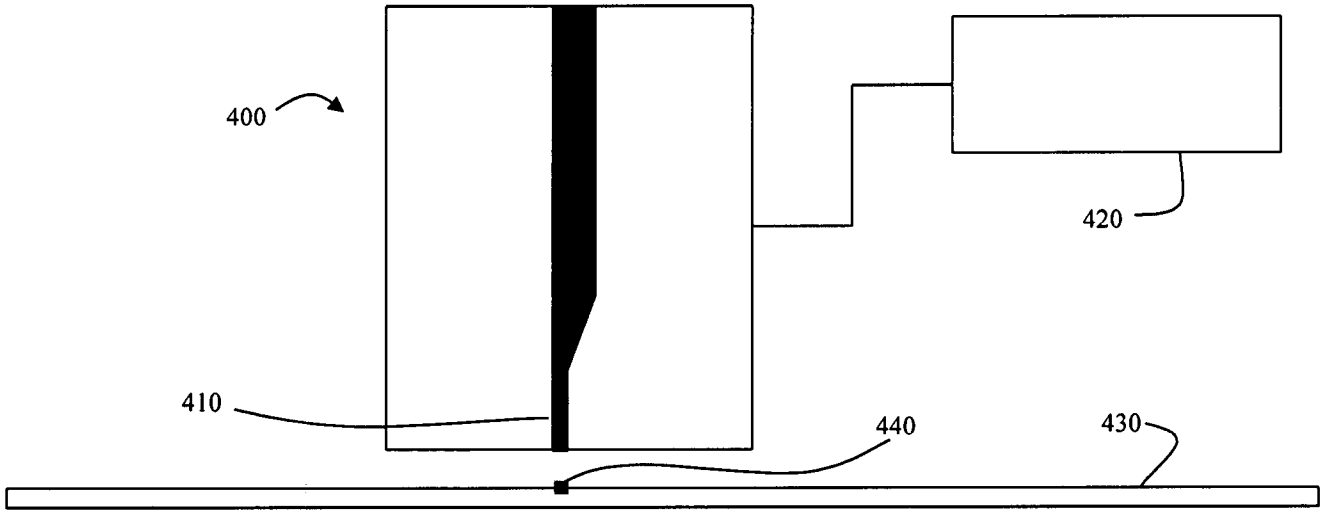


FIGURE 28A

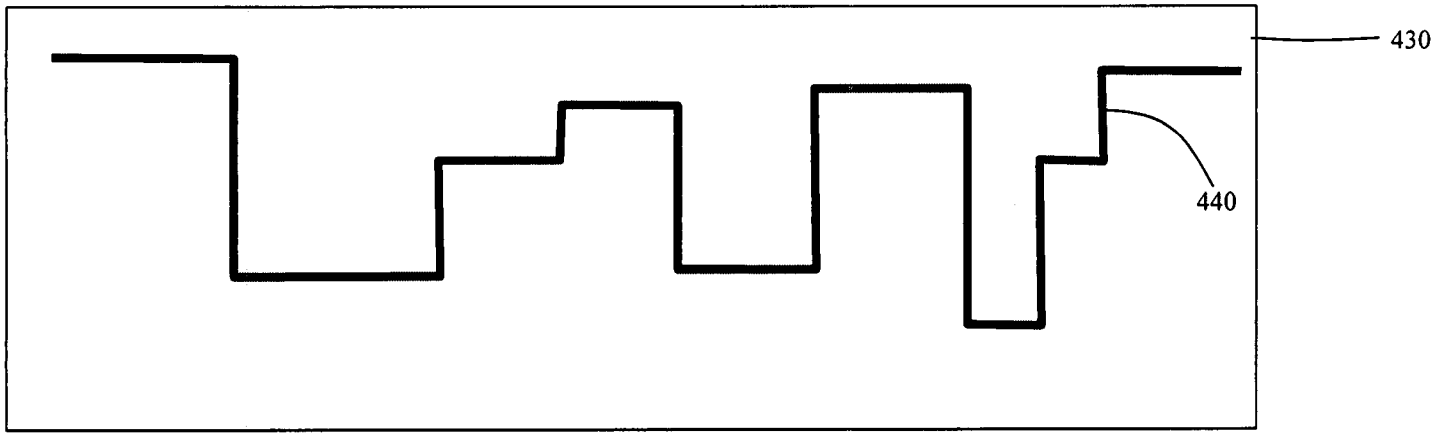


FIGURE 28B

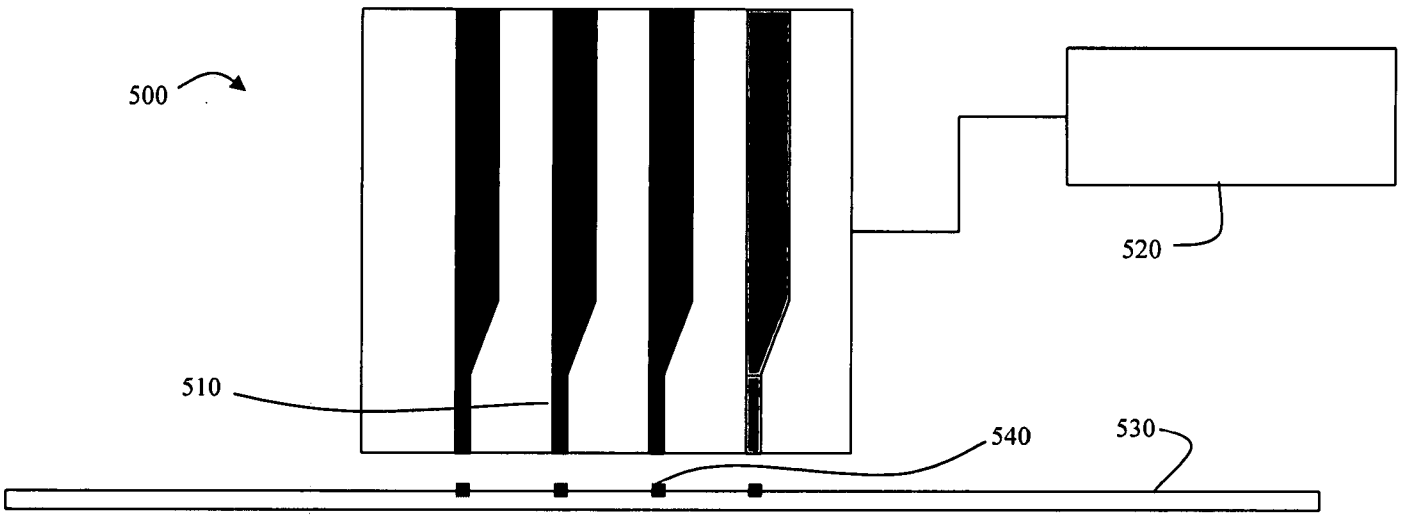


FIGURE 29A

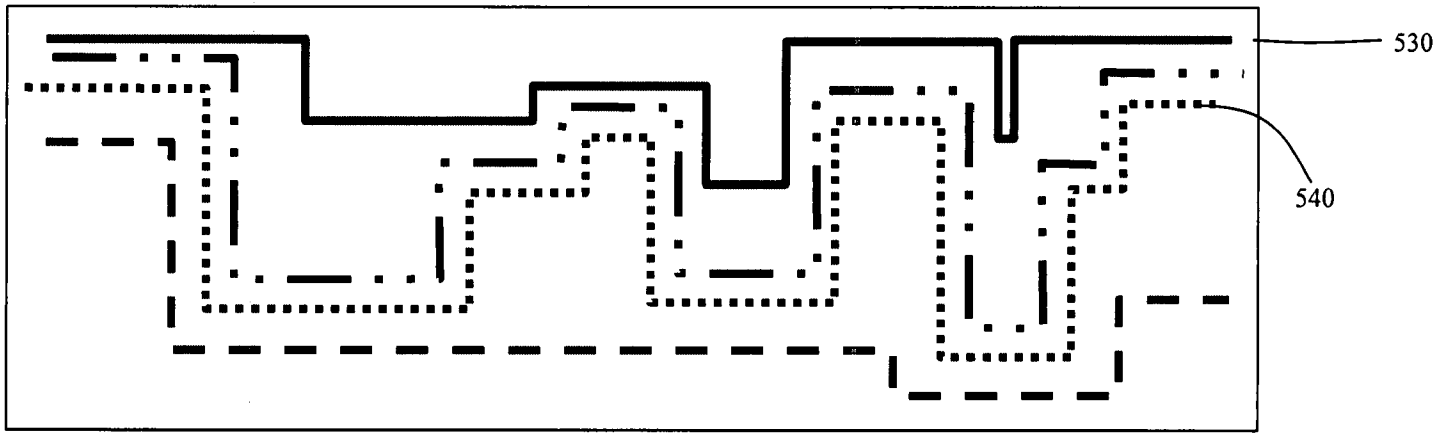


FIGURE 29B

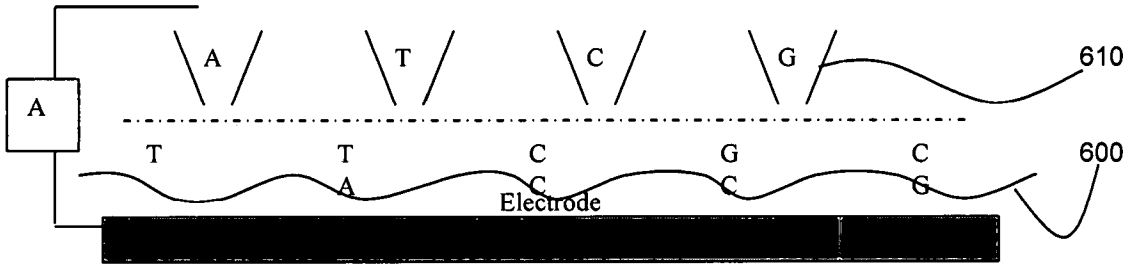


FIGURE 30

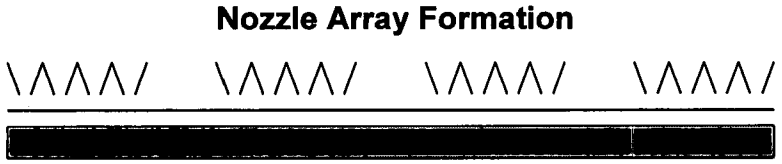


FIGURE 31

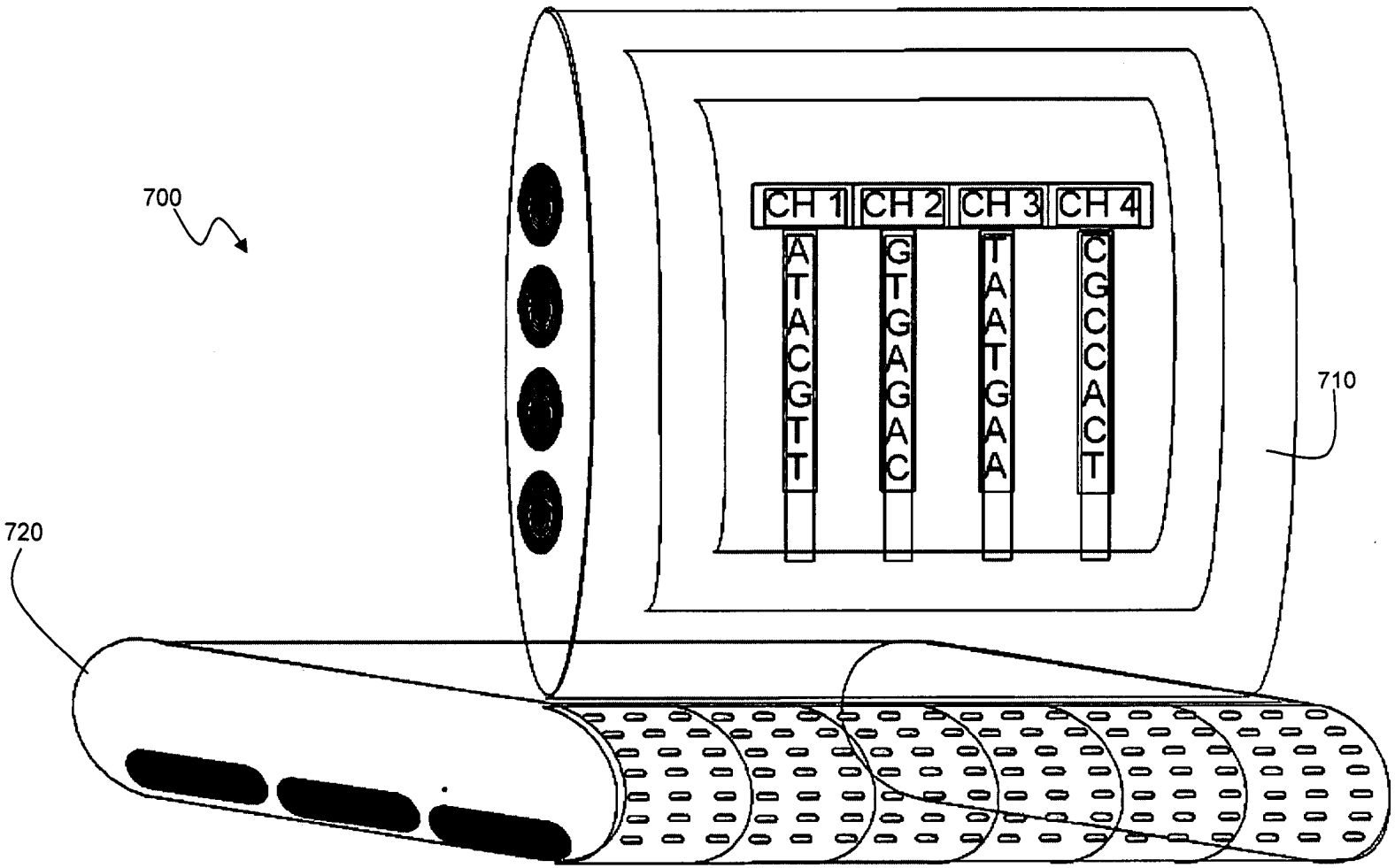


FIGURE 32

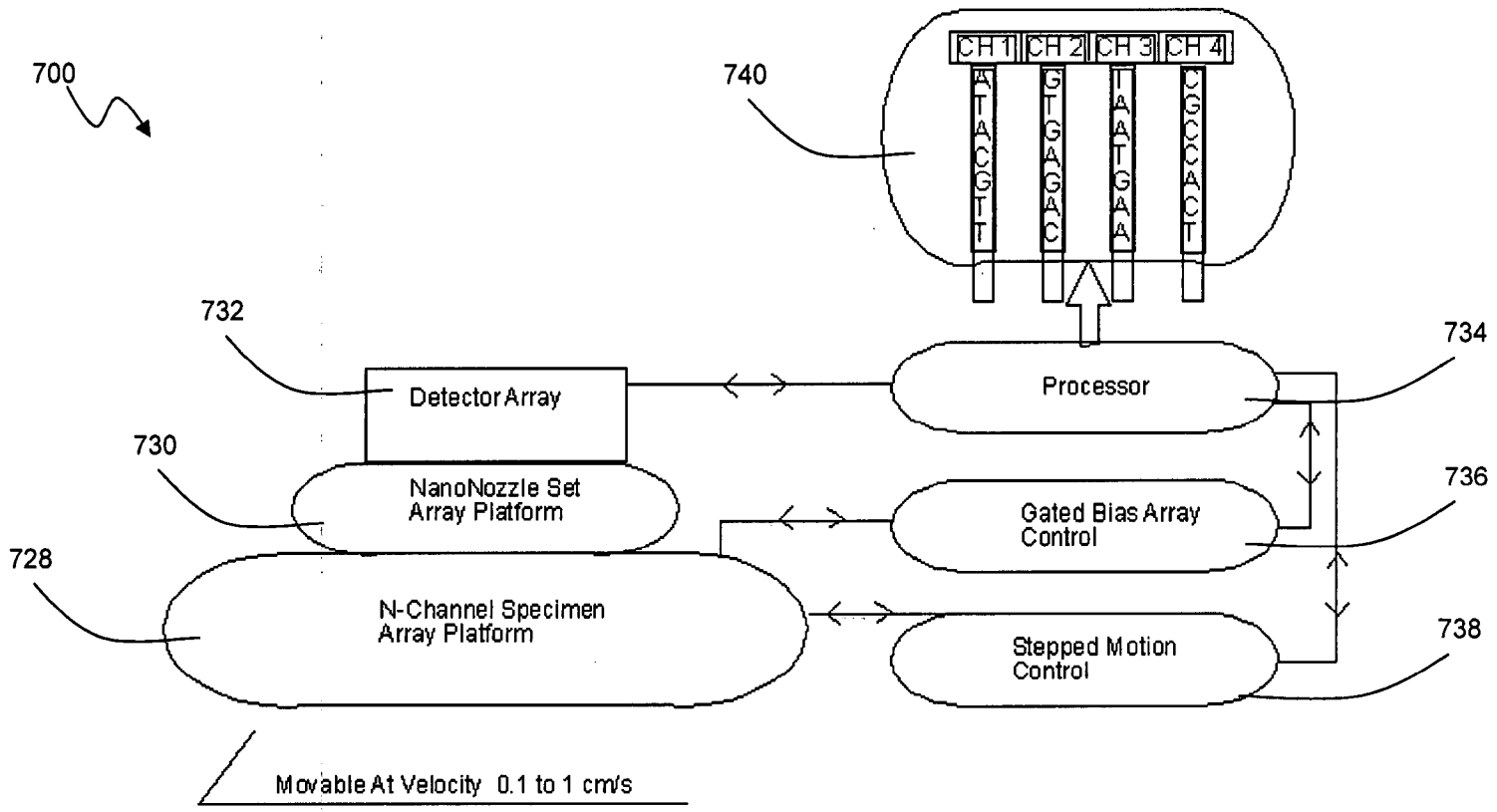

700
740
CH 1
CH 2
CH 3
CH 4
732
734
Detector Array
Processor
730
NanoNozzle Set
Array Platform
736
Gated Bias Array
Control
728
N-Channel Specimen
Array Platform
738
Stepped Motion
Control
Movable At Velocity 0.1 to 1 cm/s

FIGURE 33

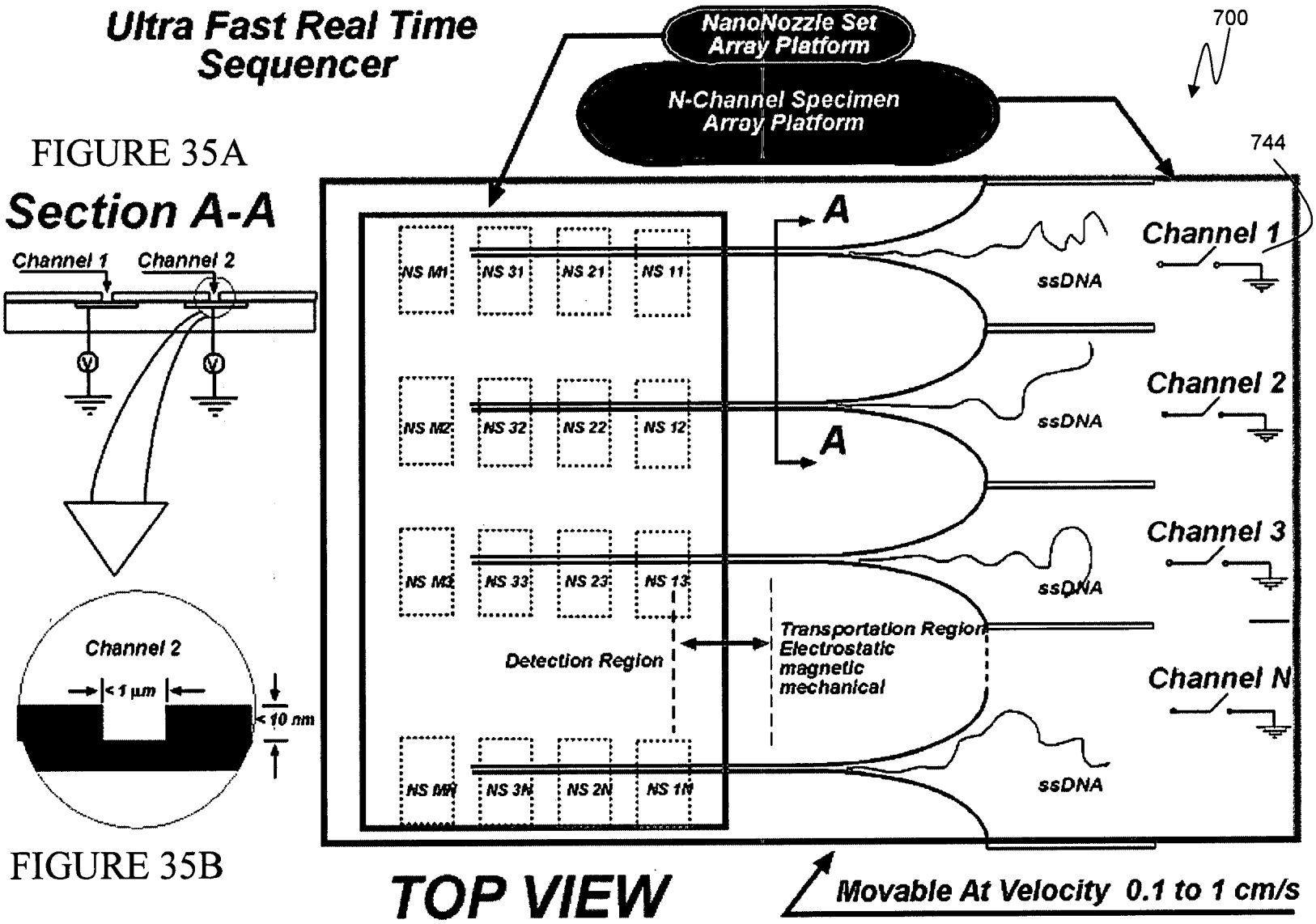


FIGURE 35A

FIGURE 35B

FIGURE 34

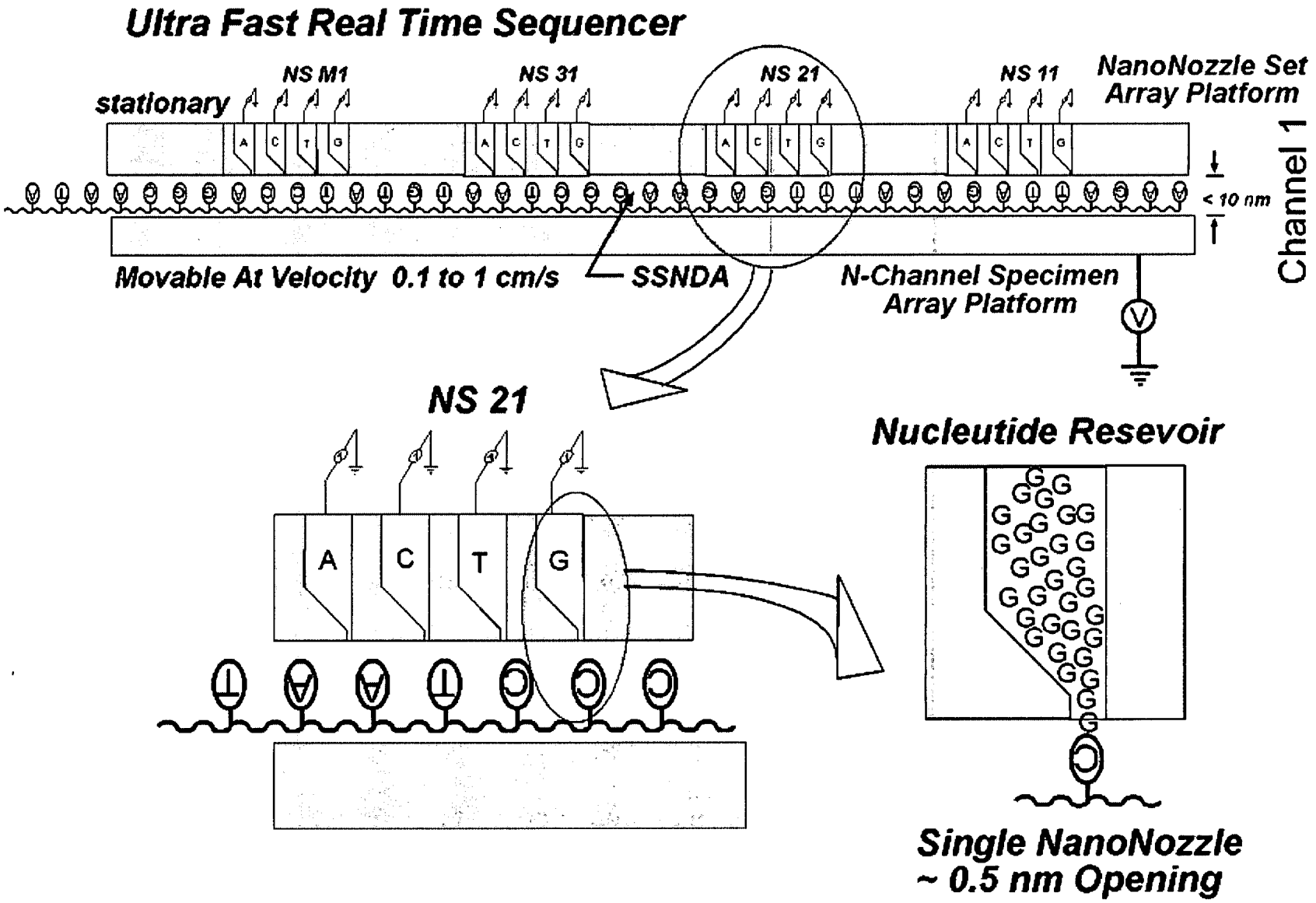

Ultra Fast Real Time Sequencer
NS M1
NS 31
NS 21
NS 11
NanoNozzle Set
Array Platform
stationary
A C T G
< 10 nm
Channel 1
Movable At Velocity 0.1 to 1 cm/s
SSNDA
N-Channel Specimen
Array Platform
V
NS 21
Nucleutide Resevoir
A C T G
Single NanoNozzle
~ 0.5 nm Opening

FIGURE 36

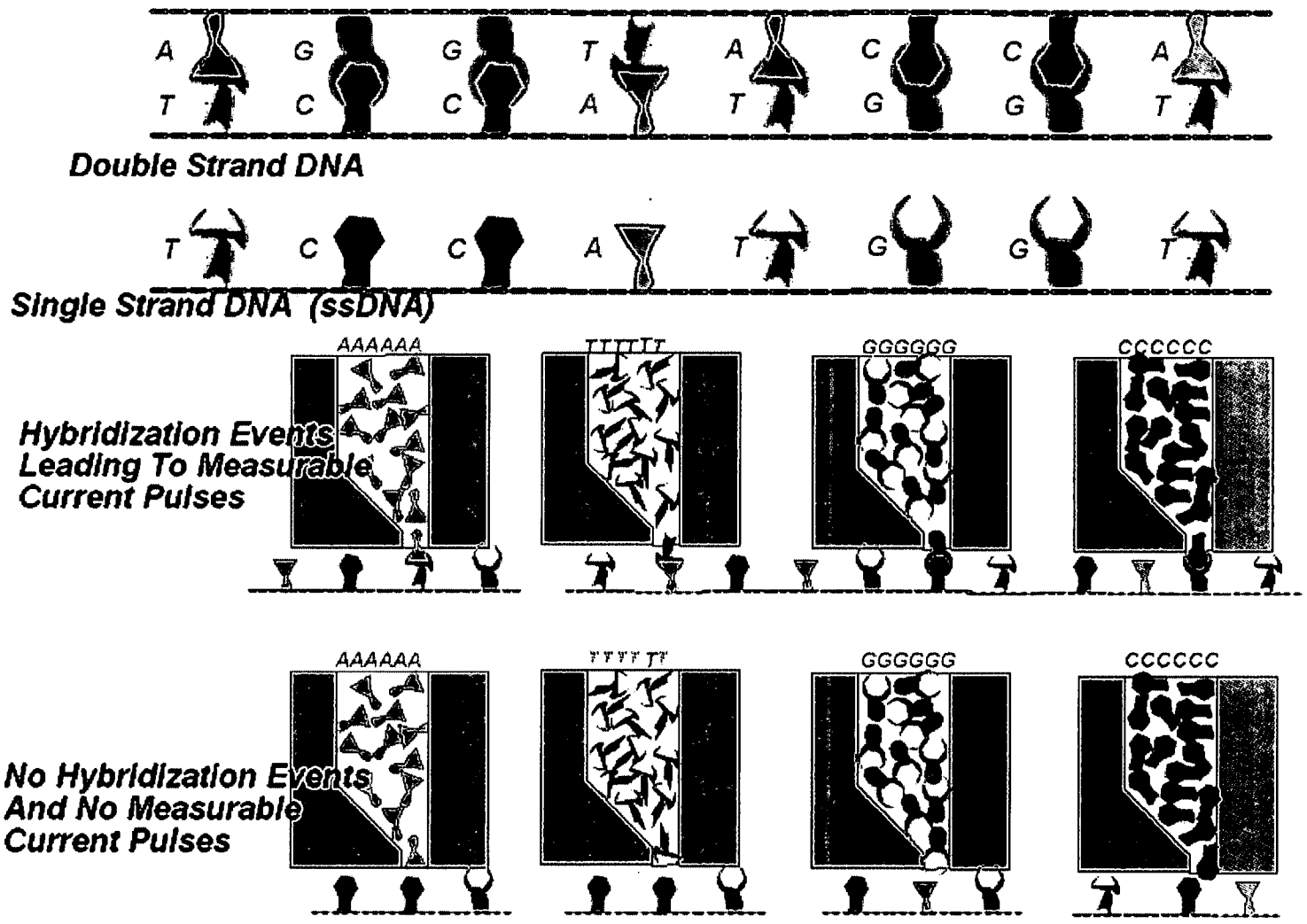

A G G T A C C A
T C C A T G G T
Double Strand DNA
T C C A T G G T
Single Strand DNA (ssDNA)
AAAAAA
TTTTTT
GGGGGG
CCCCCC
Hybridization Events Leading To Measurable Current Pulses
AAAAAA
TTTTTT
GGGGGG
CCCCCC
No Hybridization Events And No Measurable Current Pulses

FIGURE 37

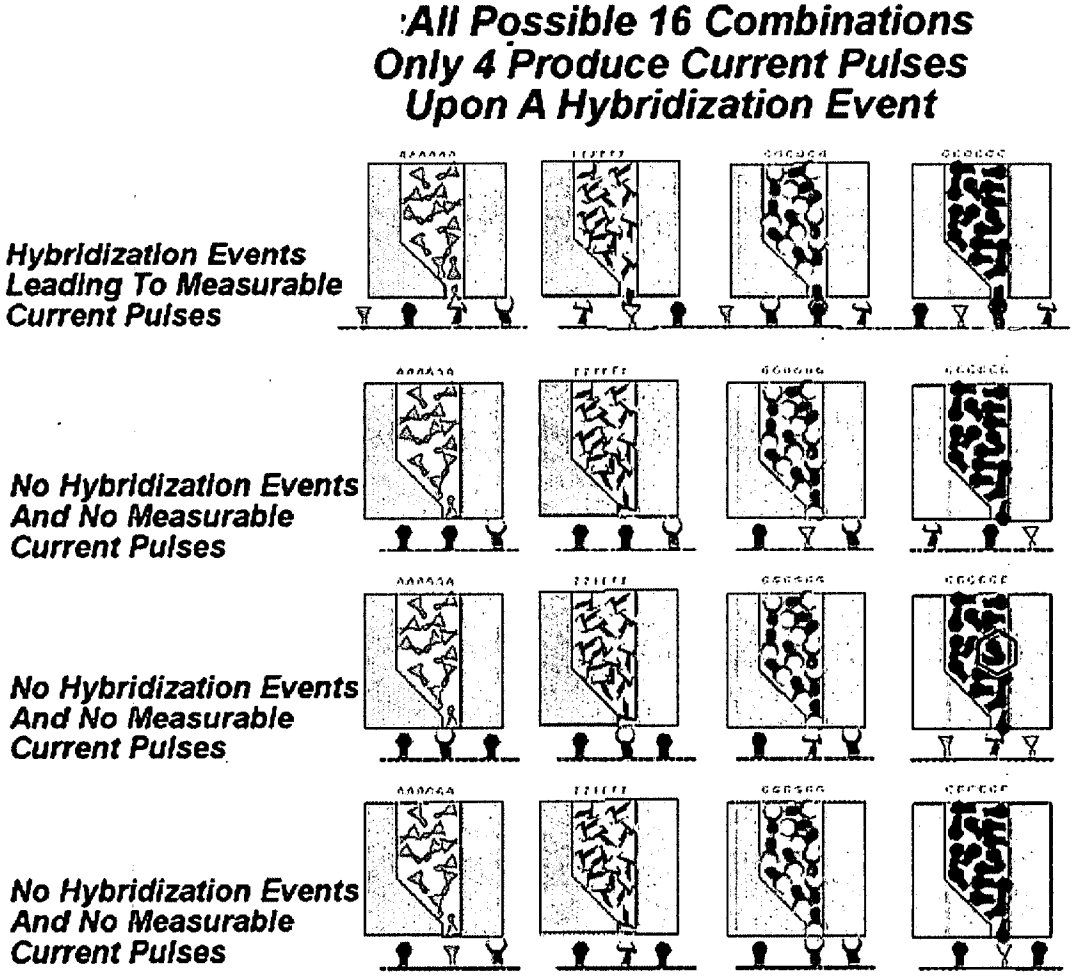

All Possible 16 Combinations
Only 4 Produce Current Pulses
Upon A Hybridization Event
Hybridization Events
Leading To Measurable
Current Pulses
No Hybridization Events
And No Measurable
Current Pulses
No Hybridization Events
And No Measurable
Current Pulses
No Hybridization Events
And No Measurable
Current Pulses

FIGURE 38

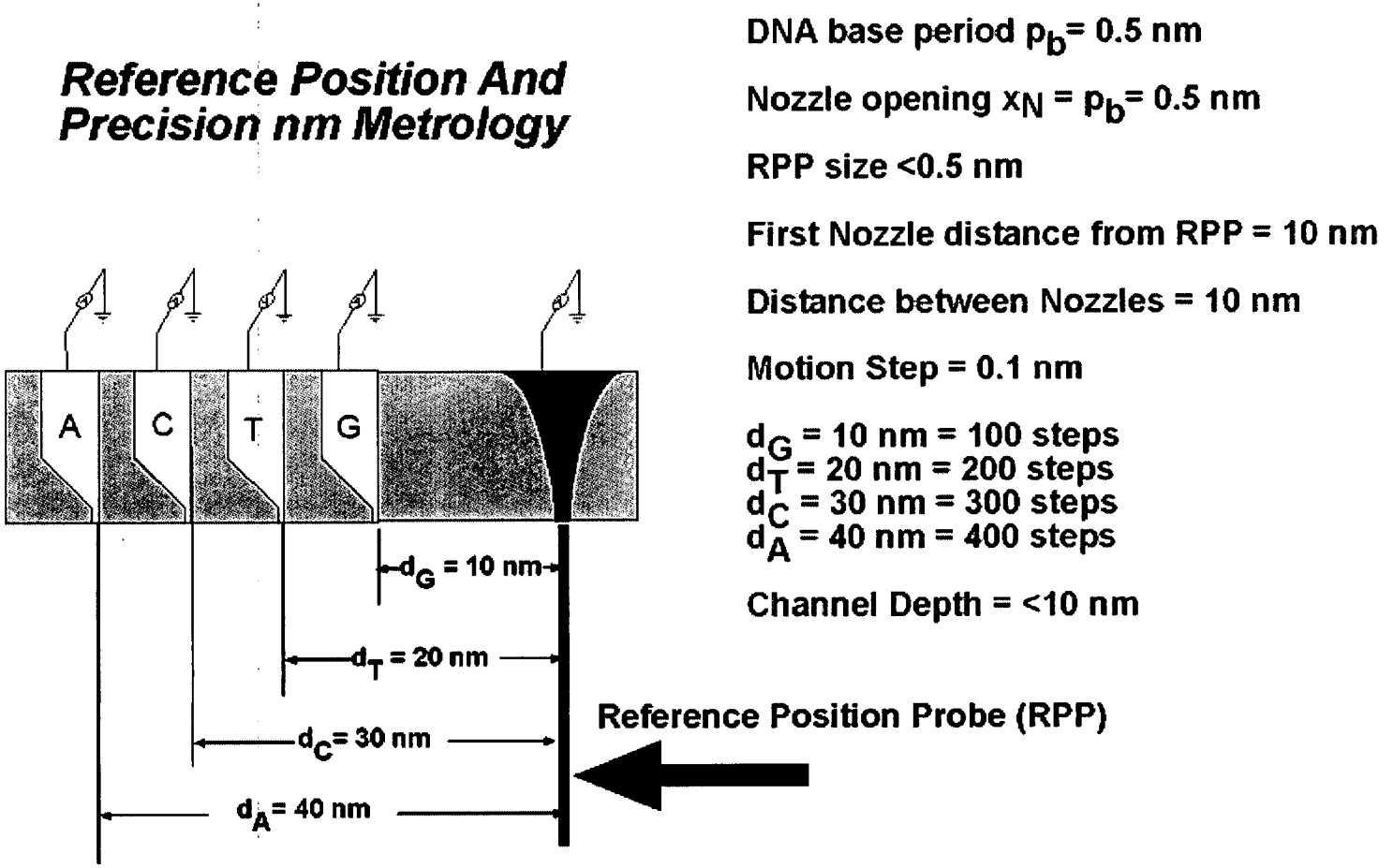

Reference Position And Precision nm Metrology
DNA base period p_b= 0.5 nm
Nozzle opening x_N = p_b= 0.5 nm
RPP size <0.5 nm
First Nozzle distance from RPP = 10 nm
Distance between Nozzles = 10 nm
Motion Step = 0.1 nm
d_G = 10 nm = 100 steps
d_T = 20 nm = 200 steps
d_C = 30 nm = 300 steps
d_A = 40 nm = 400 steps
Channel Depth = <10 nm
A
C
T
G
d_G = 10 nm
d_T = 20 nm
d_C= 30 nm
d_A= 40 nm
Reference Position Probe (RPP)

FIGURE 39

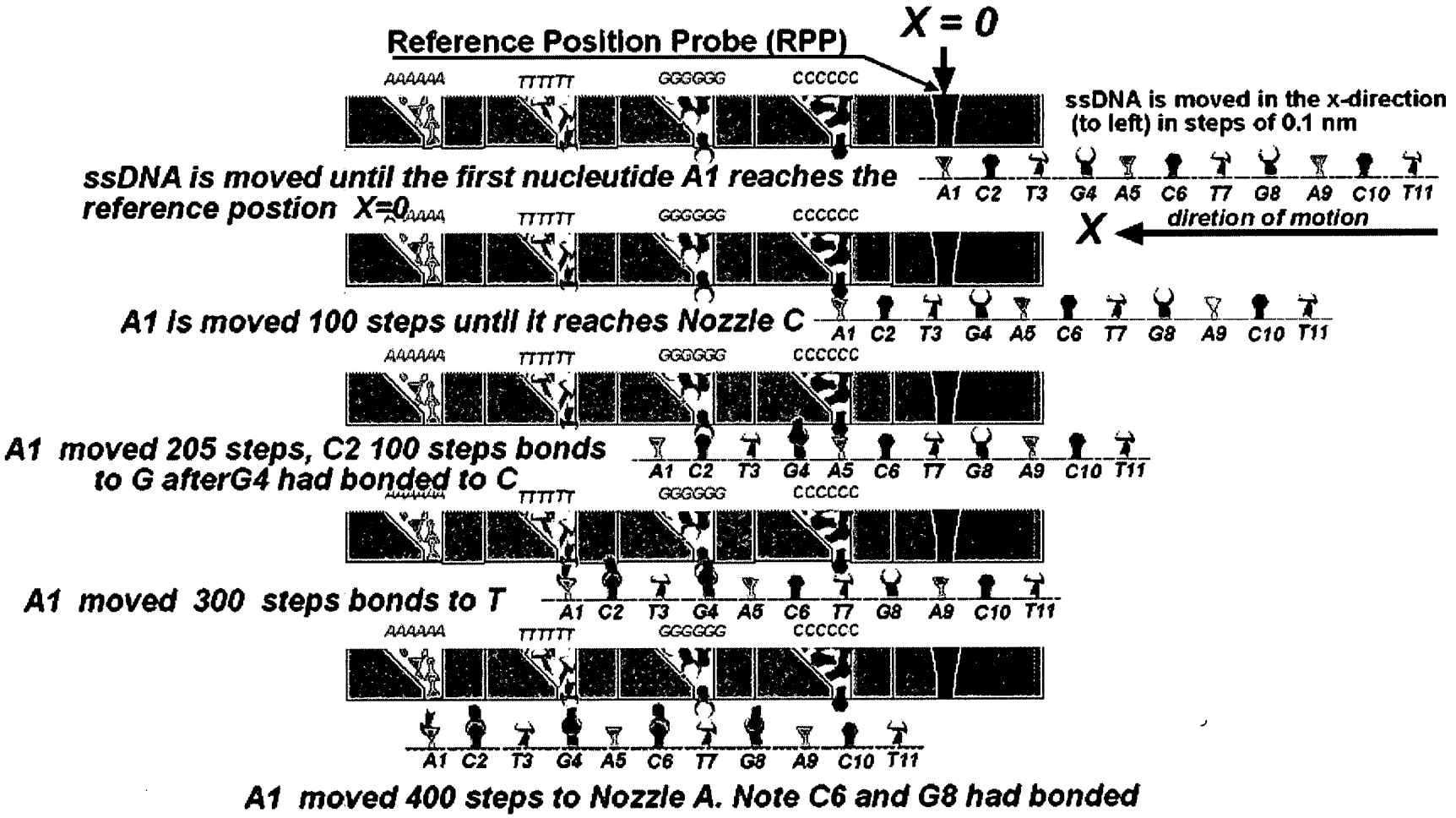

Reference Position Probe (RPP)
X = 0
AAAAAA
TTTTTT
GGGGGG
CCCCCC
ssDNA is moved in the x-direction (to left) in steps of 0.1 nm
ssDNA is moved until the first nucleutide A1 reaches the reference postion X=0
A1 C2 T3 G4 A5 C6 T7 G8 A9 C10 T11
X
diretion of motion
A1 is moved 100 steps until it reaches Nozzle C
A1 moved 205 steps, C2 100 steps bonds to G afterG4 had bonded to C
A1 moved 300 steps bonds to T
A1 moved 400 steps to Nozzle A. Note C6 and G8 had bonded

FIGURE 40